CLINICO-HEMATOLOGICAL STUDY IN PANCYTOPENIA PATIENTS PRESENTING TO TERTIARY CARE HOSPITAL

Dissertation submitted to

The Tamil Nadu Dr. M.G.R Medical University, Chennai

In fulfilment of the requirements for the award of the degree of

Doctor of Medicine in General Medicine

Under the guidance of

PROF. Dr. SARAVANAN .T, MD (GENERAL MEDICINE)

DEPARTMENT OF GENERAL MEDICINE

PSG INSTITUTE OF MEDICAL SCIENCES & RESEARCH, COIMBATORE

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY, CHENNAI, TAMILNADU

MAY 2018

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This is to certify that the dissertation entitled, **"CLINICO-HEMATOLOGICAL STUDY IN PANCYTOPENIA PATIENTS PRESENTING TO TERTIARY CARE HOSPITALS"** is the bonafide original research work of **Dr .MALLAN PRAKASH.M** under the guidance of **Dr.SARAVANAN .T, M.D,** Professor of Medicine, PSG IMS&R, Coimbatore in partial fulfilment of the requirements for the degree of Doctor of Medicine in General Medicine.

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"CLINICO-HEMATOLOGICAL STUDY IN PANCYTOPENIA PATIENTS PRESENTING TO TERTIARY CARE HOSPITAL"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. SARAVANAN .T, MD,** Professor of Medicine, PSG IMS&R, Coimbatore. This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University in fulfilment of the university regulations for the award of MD degree in General Medicine. This dissertation has not been submitted for award of any other degree or diploma.

Signature of the Candidate

Dr. MALLAN PRAKASH .M

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This is to certify that this dissertation work titled **"CLINICO-HEMATOLOGICAL STUDY IN PANCYTOPENIA PATIENTS PRESENTING TO TERTIARY CARE HOSPITALS"** of the candidate **Dr. MALLAN PRAKASH.M** with registration Number **201511504** for the award of **DOCTOR OF MEDICINE** in the branch of **GENERAL MEDICINE**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **2%** of plagiarism in the dissertation.

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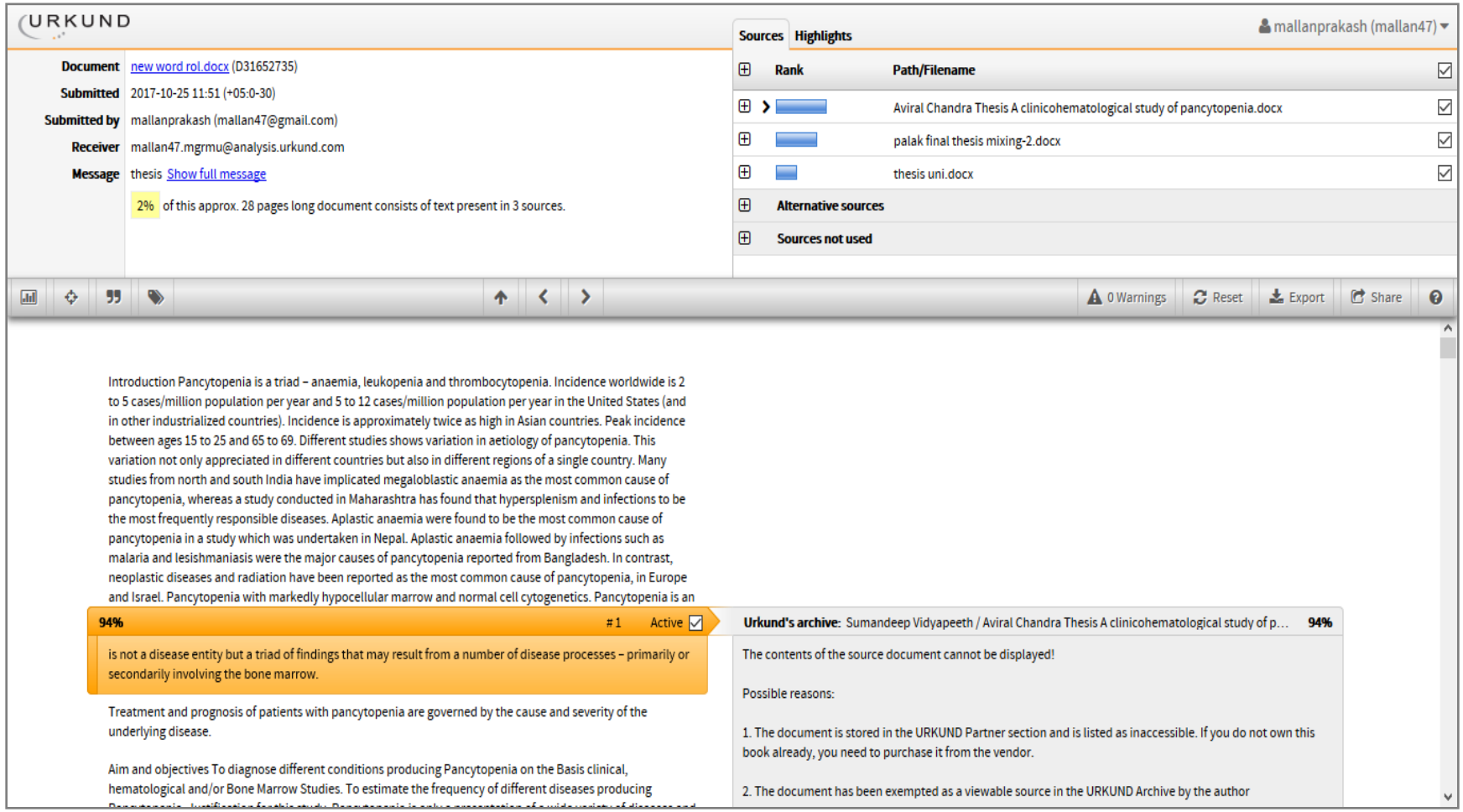
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Treatment and prognosis of patients with pancytopenia are governed by the cause and severity of the underlying disease.
Aim and objectives To diagnose different conditions producing Pancytopenia on the Basis clinical, hematological and/or Bone Marrow Studies. To estimate the frequency of different diseases producing
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INTRODUCTION

Pancytopenia is a triad – anaemia, leukopenia and thrombocytopenia. Incidence worldwide is 2 to 5 cases/million population per year and 5 to 12 cases/million population per year in the United States (and in other industrialized countries). Incidence is approximately twice as high in Asian countries. Peak incidence between ages 15 to 25 and 65 to 69 [1]. Different studies shows variation inaetiology of pancytopenia. This variation not only appreciated in different countries but also in different regions of a single country. Many studies from north and south India have implicated megaloblastic anaemia as the most common cause of pancytopenia. Aplastic anaemia were found to be the most common cause of pancytopenia in a study which was undertaken in Nepal [2]. Aplastic anaemia followed by infections such as malaria and lesishmaniasis were the major causes of pancytopenia reported from Bangladesh [3]. In contrast, neoplastic diseases and radiation have been reported as the most common cause of pancytopenia, in Europe and Israel [4]. Pancytopenia with markedly hypocellular marrow and normal cell cytogenetics. Pancytopenia is an important clinic - haematological entity encountered in our day-to-day clinical practice. It is not a disease entity but a triad of findings that may result from a number of disease processes – primarily or secondarily involving the bone marrow. Treatment and prognosis of patients with pancytopenia are governed by the cause and severity of the underlying disease [1].

AIM AND OBJECTIVES

To diagnose different conditions producing Pancytopenia on the Basis clinical, hematological and/or Bone Marrow Studies.

To estimate the frequency of different diseases producing Pancytopenia.

The justification for this study:

Pancytopenia is only a presentation of a wide variety of diseases and aetiology can be varied, depends on the geographical distribution, genetic variations, nutritional status, age and many other factors. Yet there have been not much data available on the clinic haematological study in pancytopenia in south India.

MATERIALS AND METHODS

Hospital-based prospective study

Sample size: 1-year duration [july 2016- july 2017]

Inclusion criteria:

- Both sexes, age of 18yrs and above. Haemoglobin <10g/dl. Leucocyte count <4000/cu.mm. Platelet count <100000/cu.mm [5]
- The study will be carried out on patients admitted in PSGIMSR (medical ward, IMCU, MICU) in pancytopenia patients.

Exclusion criteria:

- All patients below the age of 18yrs

The study is based on prospective collection of data in pancytopenia patient who fulfilled the inclusion criteria stated above and admitted in the medical ward in a tertiary care centre (PSGIMSR) where systematic computer coding for the registry is used.

A written informed consent was obtained from all the patients after having fully explained the purpose, protocols, and risk involved in the study. All the patients underwent a detailed medical history and full physical examination followed by blood sampling for investigations i.e complete blood count with peripheral picture, absolute reticulocyte count, erythrocyte sedimentation rate, fasting serum vitamin B12 and folic

acid level, anaemia profile, TSH, T3, T4, smear for malarial parasite, liver and renal function test, and viral markers (HBsAg, HCV, HIV), chest x-ray and ultrasonography of abdomen and/or diagnostic Bone marrow aspiration and trephine biopsy subsequently carried out under aseptic precaution after obtaining written consent from the patient or guardian. If needed Coombs test, EBV, CMV, ANA IF, ANA profile, serum lactate dehydrogenase, uric acid Rheumatoid factor, tuberculin test, serum coagulation profile, fibrinogen and D-Dimer and special investigation – like Immunophenotyping, cytogenetic, lymph node biopsy, immune electrophoresis etc. Data was entered and analyzed in statistical software. Frequency and percentage would be computed for categorical variables like age and sex distribution, physical findings, peripheral blood picture, haematological parameters and common causes leading to pancytopenia.

REVIEW OF LITERATURE

Physiology – haematopoiesis [6]

In various sites of human body, red blood cells are produce right from intra uterine period to adulthood. In the initial stage [fetus] blood cells are formed in the yolk sac followed by production of red cells in the liver. There is also some amount of production in the spleen. But after about 7 months of gestation bone marrow becomes the major site of production and is the only site of production after delivery of the fetus. Except for lymphocyte which can be produced in other organs, all other cells are produced in the bone marrow. In adult life, major areas of production in the bone marrow are those in humerus shaft, spine, femur, skull, pelvis, and thoracic cage.

The haematopoietic stems cells developed into various lineages depending upon the stem cell type. Myeloid cells gives rise to neutrophils, monocytes etc while reticulocyte give rise to RBC and megakaryocytes giving rise to platelets.

The connective tissue cells are within the trabeculae of bone along with fat cells, blood vessels, etc. these all are held together by the network of reticulin fibrils. These structures are rich in vascular sinusoids and these are the sites were newly produced cells enter. Since there are abundant fat cells in the marrow the adequate bone marrow sample is absolutely necessary for various laboratory analysis for accurate determination of details about haematopoietic stem cells [6, 7]

Obtaining bone marrow biopsy plays a pivotal role in making the diagnosis of various disorders related to the stem cells of the haematopoietic system. The sample obtained by aspiration provide finer details [morphology] compare to the histological examination of the core biopsy. The most common method used for obtaining bone marrow biopsy is the trephine method. The core biopsy provides more accurate details regarding the cellularity of the stem cells when compared to the aspirated specimen. Therefore both the specimen [aspiration and core biopsy] are needed to make a more accurate diagnosis.

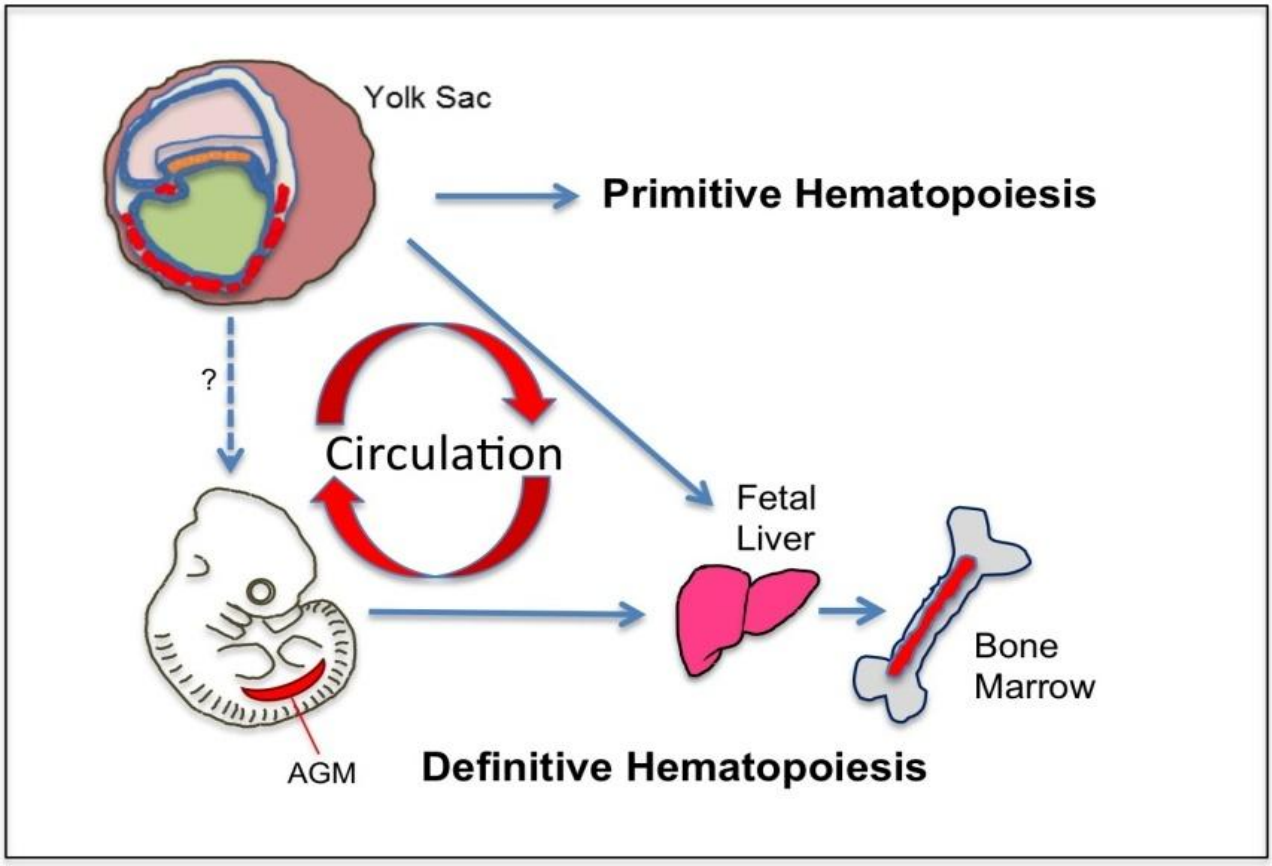


Figure 1: Primitive and definitive haematopoiesis[AGM - aorta-gonads-mesonephros, HSC - hematopoietic stem cells]

- Primitive hematopoiesis - blood stem cells differentiate into only a few specialized blood lineages (typically isolated to early fetal development)
- Definitive hematopoiesis - multipotent HSCs appear (occurs through the majority of the human lifetime) [8].

Table 1:Bone marrow examination indications [9]

1. Unexplained anaemia, abnormal red cell indices, cytopenias or cytoses
2. Abnormal peripheral blood smear morphology suggestive of bone marrow pathology
3. Diagnosis, staging and follow up of malignant haematological disorder
4. Suspected bone marrow metastases
5. Unexplained focal bony lesion on radiological imaging
6. Unexplained organomegaly or presence of mass lesion inaccessible for biopsy
7. Microbiological culture for investigations of pyrexia of unknown origin or specific infection, e.g – miliary tuberculosis, leishmaniasis, malaria
8. Evaluation of iron stores
9. Investigation of lipid/glycogen storage disorders
10. Exclusion of haematological disease in potential allogeneic stem cell transplant donors

Preliminary procedures [10]:

- The procedure should be explained in detail to the patient. The past clinical history of the patient should be obtained
- Informed consent should be obtained from the patient
- A blood count and smear should be obtained if these have not been collected in the previous 2 days

Anatomical sites – preferred site is posterior iliac crest in adults and medial surface of the tibia in infants. Another site also useful in special circumstances – anterior iliac crest in immobile patients, sternal aspiration when patient receive radiotherapy to the pelvis and other site have a dry tap or core biopsy is not required. In obese patient computed tomography-guided marrow sampling is useful when difficult to localize iliac crest [11].

Bone marrow aspirate:

Review the patient identification before starting procedure. If posterior iliac crest is chosen a site, patient placed in left or right lateral position or prone position. Sterilize the site with the sterile solution, place a sterile drape over the site, and administer local anaesthesia, infiltrate the skin, soft tissues and periosteum. After giving anaesthesia, make an incision through which you can introduce the bone marrow aspiration needle. The needle should be advance at an angle completely perpendicular to the bony prominence of the iliac crest. Once needle passes through the cortex end enters the marrow cavity, it should stay in place without being held. Remove the stylet and aspirate approximately 1 ml of bone marrow aspiration into a syringe. If specimen shows

spicules; the assistant should use it to make smear slides immediately. If spicules are sparse or not present, a new sample should be obtained from a slightly different site [10]

Bone marrow biopsy:

The same skin incision to use to perform core biopsy, and adjust the needle for inserting at a different angle into bone. Needle introduce in a clockwise rotation with a stylet, after entering into periosteum remove the stylet and advance the needle with a clockwise motion to a depth of 2 cm. Then twist the needle clockwise and counter-clock wise several times and rock it gently back and froth in multiple directions, then slowly remove from bone. Then use a probe to remove the marrow from the needle. In adult adequate specimen is approximately 2 cm long. Apply pressure to obtain adequate haemostasis, then clean the area with alcohol. Place clean or antibiotics – soaked gauze at the incision site and using a compression bandage. The bandage may be removed after 24hrs; once the bandage is removed, the area should be monitor for infection or delayed bleeding [10]

Marrow cellularity:

Cellularity may be altered as increased, normal or reduced at the time of inspecting stained film containing marrow particles

- <25% particle – hypocellular
- 75-80% - hypercellular

Ratio:

Myeloid:erythroid ratio based on a count of 200-500 marrow cells. Normal adult ratio 3 or 4:1

Table – 2: Various cell composition of adult bone marrow aspirate

Cells	**95% range**	**Mean [16]**	**Mean [17]**
Myeloblast	0-3	0.4	1.4
Promyelocytes	3-12	13.7c	7.8
Myelocyte	2-13	-	7.6
Metamyelocytes	2-6	-	4.1
Neutrophils	22-46	35.5	32.1; 37.4
Myelocyte	0-3	1.6	1.3
Eosinophils	0.3-4	1.7	2.2
Basophils	0-0.5	0.2	0.1
Lymphocyte	5-20	16.1	13.1
Monocytes	0-3	2.5	1.3
Plasma cells	0-3.5	1.9	0.6
Erythroblasts	5-35	23.5	28.1; 22.5
Megakaryocytes	0-2		0.5
Macrophages	0-2	2	0.4

Table – 3:Various staining patterns of different cellular material

Cellular component	Colour
Nucleoli	
Chromatin	Purple
Nucleoli	Light blue
Cytoplasm	
Reticulocyte	Grey blue
Erythroblast	Dark blue
Lymphocyte	Blue
Erythrocyte	Dark pink
Metamyelocyte	Pink
Monocyte	Grey blue
Myelocyte	Pink
Neutrophil	Orange/pink
Promyelocyte	Blue
Basophil	Blue
Granules	
Promyelocyte	Red or purple
Eosinophil	Red or orange
Basophil	Purple-black
Neutrophil	Purple

Toxic granules	Dark blue
Platelet	Purple
Other inclusion	
Auer body	Purple
Cabot ring	Purple
Howell-jolly body	Purple
Dohle body	Light blue

Marrow flim stainings:

Romanowsky stain is commonly used for staining of blood films, and a good result can be obtained. The property of romanowsky dyes unique to it is of making small distinction in shaes of staining, and of staining different granules on various shades, depend on 2 components: azure B [trimethylthionin] and eosin Y [tetrabromo-fluorescein [12, 13]

Contraindications:

No absolute contraindications, but relative contraindications are related to the general condition of the patient or risk of anaesthesia. An active infection at the proposed site of aspiration.

Table – 4: Complication of bone marrow aspiration & biopsy [14]

- Trauma to neighboring structures and soft tissues
- Infection
- Retroperitoneal haemorrhage
- Fractures of underlying bone [patient with osteoporosis]
- Cardiac tamponade in sternal aspiration [N-1]

Risk factors for haemorrhage

- Thrombocytopenia, concurrent use of anticoagulants and the presence of myeloproliferative disorder.

Diagnostic utility of bone marrow sampling in HIV positive patients[15]:

Bone marrow sampling used in pyrexia of unknown origin without localizing signs, pancytopenia, and staging/investigation of lymphoma. Of 122 bone marrow samples taken to investigate pyrexia, 33 [22%] revealed the cause on microscopy: unexpected lymphoma in seven [6%], mycobacteriosis in 25 [20%], and toxoplasmosis – 1 [1%]. Marrow infiltration was confirmed in 11 of 38 bone marrow samples taken for staging/investigation of lymphoma/leukemia. In afebrile patients, of 22 with pancytopenia, bone marrow sample showed HIV associated changes in 17 and specific diagnoses in 5 [3- mycobacterial infection, 1- haemophagocytic syndrome, and 1-

vitamin b12 deficiency]; of 21 with isolated thrombocytopenia, 20 [95%] bone marrow sample showed immune thrombocytopenic purpura to be the cause and the remaining patient had bone marrow changes of aplasia; of 29 with isolated anaemia, 28 had bone marrow changes of HIV associated dysplasia/erythroid dysplasia and 1- had unsuspected iron deficiency anaemia; all 10 with isolated leukopenia/neutropenia had bone marrow changes ascribed to HIV infection exacerbated by concurrent sepsis or medication; of 4 bone marrow samples taken for other reasons, 1- showed mycobacterial infection.

Aetiology of pancytopenia

Hypocellular marrow:

- acquired aplastic anaemia
- inherited aplastic anaemia [fanconi anaemia and others]
- some myelodysplasia syndrome
- rare aleukemic leukemia [acute myeloid leukemia]
- some acute lymphoblastic leukemia
- rare lymphomas of bone marrow

Hypercellular marrow:

- vitamin b12, folate deficiency, alcohol
- primary bone marrow diseases
- myelodysplasia syndrome
- paroxysmal nocturnal hemoglobinuria
- myelofibrosis

- some aleukemic leukemias
- myelopthisis
- bone marrow lymphoma
- hairy cell leukemia
- secondary to systemic diseases, overwhelming infection
- systemic lupus erythematosus, sjogren syndrome, hypersplenism
- brucellosis, sarcoidosis, tuberculosis and atypical mycobacteria

Macrocytic anaemia [16]

Macrocytosis refers to red blood cells larger than usual. It is strictly a morphologic term and does not imply a specific pathophysiology. Macrocytosis can be documented using the mean corpuscular volume from an automated hematology instrument, measured in femtoliters (fL; 10^{-15} liter) or by observing larger-than-normal RBCs on the peripheral blood smear.

Macrocytosis is defined as an MCV above the upper limit of normal, which varies by age:

- Preterm infants born at ≤25 weeks of gestation – 119 ± 7 fL
- Term newborns (cord blood) – 106 ± 4 fL
- Infants and young children – 90 fL
- Adults – 96 to 100 fL (the higher value may be more appropriate for older adults)

RDW

RBC distribution width is a measure of the variation in RBC sizes. A single uniform population of RBCs will have a normal RDW regardless of whether the absolute MCV is normal or abnormal. A population of RBCs with varied sizes or two populations of RBCs (eg, small RBCs plus reticulocytes) will have a large RDW.

Large RBCs on peripheral blood smear

RBC size on the peripheral blood smear is estimated by comparing RBCs to the nucleus of a small lymphocyte. The normal RBC diameter on the peripheral blood smear is 7 to 8 microns, approximately the size of the nucleus of a small lymphocyte; RBCs that have a greater diameter are considered macrocytic.

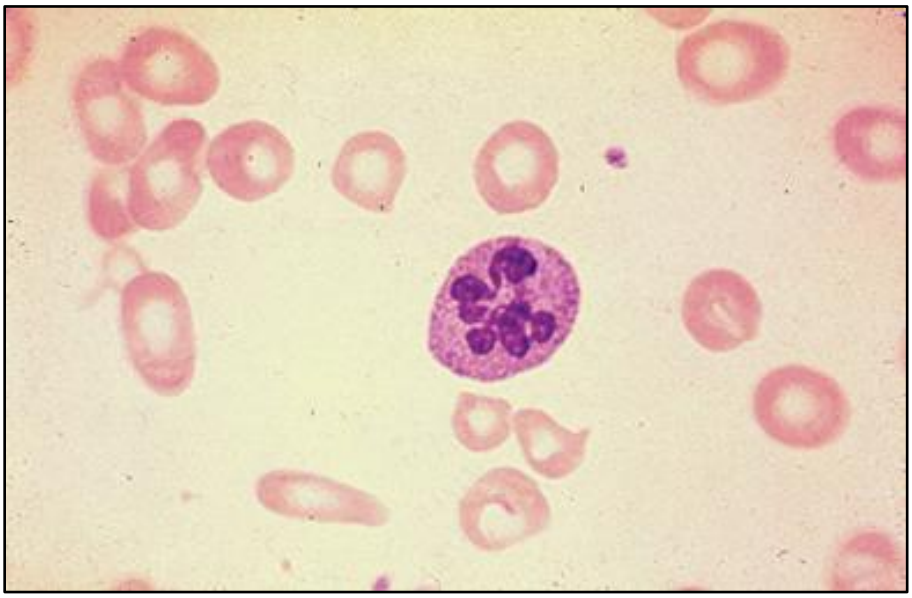


Figure – 2: Peripheral blood smear showing a hypersegmented neutrophil (seven lobes) and macro-ovalocytes

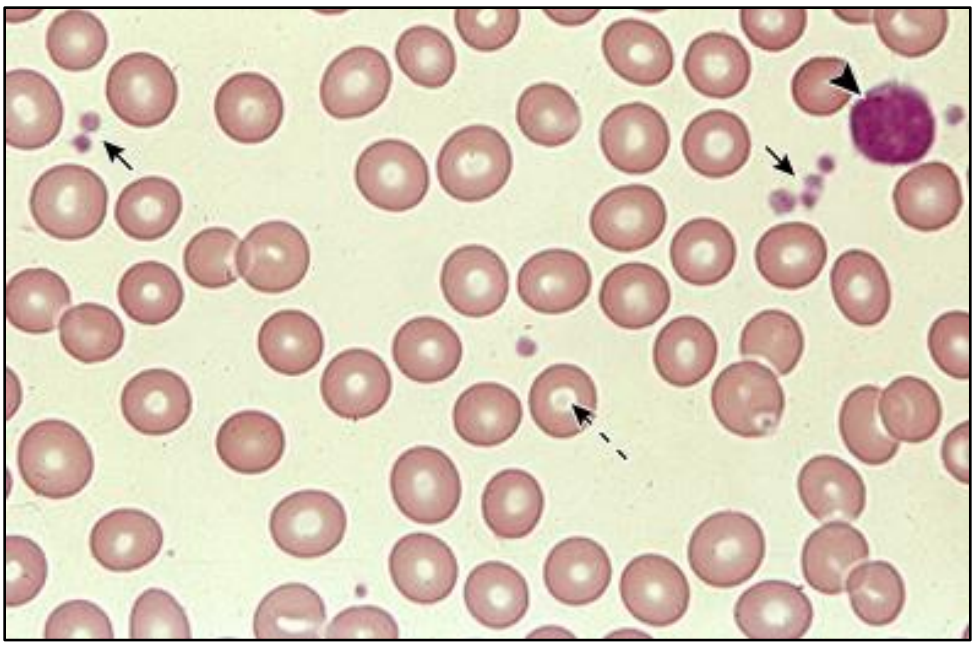


Figure – 3: High-power view of a normal peripheral blood smear. Several platelets (arrows) and a normal lymphocyte (arrowhead) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter

Hypersegmentation of neutrophils signifies megaloblastic “arrest” and thus impaired DNA synthesis. The following are the feature of hypersegmentation

- Any neutrophil with 6 or more lobes
- 5% of neutrophils with 5 lobes
- Majority have more than 4 lobes

A lobe is considered distinct if it is separate from the nucleus or connected by a fine chromatin thread. It has been suggested that hypersegmentation can be most reliably detected by use of the segmentation index (% of neutrophils with five lobes or more, relative to the number of four-lobed neutrophils).

Other diseases associated with Hyper segmented neutrophils are as follows

1. Iron deficiency anaemia [35, 36]
2. Uraemia [37]
3. Hyperthermia [38]
4. Myelodysplastic syndromes [39]
5. Langerhans cell histiocytosis [40]
6. Post irradiation [41]
7. Drugs such as chemotherapeutic agents, steroids [42], granulocyte colony stimulating factor.

Pathophysiology:

Red blood cells leave the bone marrow as reticulocytes, which are macrocytic. All other macrocytic RBCs are formed as a consequence of inherited or acquired abnormalities in RBC maturation, nucleic acid metabolism, membrane composition, cell water content, or a combination of these factors [17, 18, 19].

1. Increased reticulocytes
2. Abnormal RBC development
3. Abnormal RBC membrane

Reticulocytosis can occur in any of the following settings:

- Any hemolytic anemia
- Repletion of iron, vitamin B12, folic acid, or copper
- Recovery from bleeding or transient bone marrow aplasia (eg, following parvovirus infection)
- Any other condition associated with increased erythropoietin, such as congenital heart disease, erythropoietin-secreting tumors, or "blood doping"

Table – 5: Differential diagnosis of macrocytosis

Megaloblastic	Nonmegaloblastic	False elevation
• atrophic gastritis • enteral malabsorption • HIV treatments • Anticonvulsants • Primary bone marrow disorder • Nitrous oxide abuse • Inherited disorder	• Alcohol abuse • Drugs abuse • Myelodysplasia • Hypothyroidism • Liver disease • Haemolysis • Haemorrhage • COPD • Splenectomy	• Cold agglutinins • Hyperglycemia • Marked leukocytosis

Table 1. Prevalence of Major Causes of Macrocytosis in Studied Populations

Etiology	Study population: Hospitalized patients in New York City[3] (%)	Outpatients in Finland[1] (%)	Finnish persons older than 75 years[4] (%)	Finnish and American patients[5] (%)
Alcohol	26	65	15	36
B_{12} and/or folate deficiency	6	9	28	21
Medications	37*	3	2	11
Hypothyroidism	—	1	12	5
Bone marrow dysplasias	6	1	5	5
Liver disease (nonalcoholic)	6	—	2	6
Reticulocytosis	8	—	—	7
Miscellaneous	3	21	13	7
Not established	7	—	22	12

NOTE: *Etiologies listed from most to least common.*

**—13 percent from zidovudine (Retrovir).*

Information from references 1 and 3 through 5.

Table – 6: Drug-induced macrocytosis [20-31]:

Megaloblastic changes:	**Reduces folate absorbtion:**
Allopurinol, Azathioprine, Capecitabine, Cladribine ,Cytosine arabinoside (ara-C), Fludarabine, Fluorouracil, Gadolinium, Gemcitabine, Mercaptopurine, Lamivudine, Leflunomide, Zidovudine, Hydroxyurea, Mycophenolate mofetil, Methotrexate, Nitrous oxide, Stavudine, Pentostatin, Teriflunomide, Trimethoprim, Thioguanine	Aminosalicylic acid, Ampicillin and other penicillins, ChloramphenicolErythromycin, Estrogens or hormonal contraceptives, Metformin, Tetracyclines, Nitrofurantoin, Phenytoin

Reduces B12 absorbtion: Proton pump inhibitors (eg, omeprazole, lansoprazole), Antacids, Histamine H2 receptor antagonists (eg, cimetidine, ranitidine, famotidine, nizatidine)	**Hemolysis in G6PD deficiency:** Methylene blue, Pegloticase, Primaquine, Dapsone, Rasburicase
Unknown: Primidone, Sunitinib, ImatinibTriamterene, Valproic acid	

Of these, most commonly see macrocytosis from hydroxyureafor sickle cell disease, chemotherapeutic agents, and antiretroviral therapy (ART) in patients with human immunodeficiency virus (HIV) infection.

Alcohol/liver disease:

Alcohol-induced macrocytosis occurs even in patients who are folate and cobalamin replete and do not have liver disease. Abstinence from alcohol results in resolution of the macrocytosis within two to four months. Return of the MCV to normal also confirms the diagnosis.

The mechanism of alcohol-induced macrocytosis is unknown. Acetaldehyde, a metabolic breakdown product of alcohol, is capable of inducing membrane changes in red blood cell (RBC) precursors and circulating RBCs of individuals with alcohol-associated

macrocytosis, through the in vivo production of aldehyde adducts [32]. Acetaldehyde also interferes with cell division and may increase cell volume by this mechanism [33].

Other forms of liver disease not related to alcohol may cause macrocytosis by effects on the lipid composition of the RBC membrane [17].

Hypothyroidism:

Macrocytosis can occur in the setting of hypothyroidism. The mechanism is unclear and may be multifactorial in some patients.

In a series of 202 patients with hypothyroidism from 1976, anaemia was present in 53 (26 percent) [34]. A subset of 53 individuals who were analyzed in more detail had macrocytosis despite normal levels of vitamin B12, folate, and iron. Of these, 13 (25 percent) had anaemia that resolved upon treatment with thyroxine. All of the remaining patients (ie, those with hemoglobin and/or MCV in the normal range) also had a decrease in MCV following thyroxine administration. Patients with autoimmune hypothyroidism may have concomitant vitamin B12 deficiency caused by autoantibodies to gastric parietal cells. In the series of 202 patients, 10 of 118 (8.5 percent) had concomitant pernicious anemia.

The typical MCV in hypothyroidism is mildly increased (in the range of 90 to 100 fL), which may be due to concomitant defects that cause macrocytosis and microcytosis (eg, B12 deficiency plus iron deficiency) [34]. This finding suggests that it may be

worthwhile to measure vitamin B12 level in individuals with hypothyroidism who are anaemic.

Diagnosis of megaloblastic anaemia:

Determining the level of vitamin B12 in the serum is the preliminary step in evaluation of megaloblastic anaemia. Quantaphase Radio II assay which is an older and non - automated protein binding method was subjected to various studies, has a sensitivity of 95-97% [43]. Nowadays it can be done in a fully automated method.This method is expected to have sensitivity at least as that of the non-automated method. Excluding wholly vitamin B12 deficiency in-spite of normal levels of B12 in the serum is not entertained.

The following are the conditions in which there would be normal or high serum vitamin B12 levels even in the face of deficiency

1. Renal failure
2. Liver disease
3. Chronic myeloid leukaemia (CML) and also other myeloproliferative disorders
4. Chronic exposure to nitrous oxide
5. Congenital transcobalamin II deficiency
6. Inborn errors of intracellular B12 metabolism
7. Parenteral therapy with Vitamin B12 supplements

Earlier studies in patients who are elderlyhave shown that increase of serum methyl malonic acid (MMA) and plasma total homocysteine (tHCYS) which are the Vitamin B12-related metabolites, in a decent fraction of cases with low normal and high normal B12 levels. In a study 35% of study population with low-normal B12 levels, i.e. 140–258 ng/l, and 24% of study population with high normal levels, i.e. >258 ng/l, had increased levels of serum methyl malonic acid and plasma total homocysteine; the corresponding figures for increased MMA only were 12 and 11% respectively [44].

Therefore, some investigators have suggested that vitamin B12 status should be fully investigated below a serum B12 level that is quite higher than the lower 95% upper limit for this vitamin.

Some of the conditions are often found to be associated with reduced vitamin B12 assay levels in spite store of the vitamin is well with in normal

1. Pregnancy
2. HIV infection
3. Folate deficiency
4. Patients on anticonvulsant drugs
5. Myeloma
6. Transcobalamin I deficiency
7. Unexplained

15% of all patients with low serum B12 levels and 15% of patients with low levels in patients without B12 malabsorption or metabolite abnormalities likely to occur due to

mild and, occasionally, severe TC I deficiency [45]. Diagnosis of the presence of Transcobalamin I deficiency is made by Radio immune assay.

Methylmalonic acid and plasma total homocystreine levels are increased in the face of vitamin B12 deficiency. The problem with Methylmalonic acid assay is that it is expensive, not widely available and a long turnaround time. Methylmalonic acid assay is highly specific for B12 deficiency provided that renal function has been ruled out. 2% of cases with folate deficiency and 98% with vitamin B12 deficiency have elevated Methylmalonic acid levels [46]. Homocysteine assays are less expensive but the availability is wider when compared to serum Methylmalonic acid assays. The sensitivity of homocysteine assay is 96% 37 and 91% in cases of B12 and folate deficiency respectively. It is useful in patients with in renal failure, alcohol abuse, vitamin B6 deficiency, hypothyroidism, patients receiving certain drugs (e.g. isoniazid) and inborn errors of homocysteine metabolism. The increased methylmalonic acid and homocysteine levels in B12 deficiency return to normal after treatment with B12 but not with folate [47].

Holotranscobalamin II (holo-TC II)

Only 6–20% of the B12 in serum is bound to transcobalamin II (TC II), the transport protein involved in delivering B12 to cells; the remainder is bound to transcobalamin I (haptocorrin) whose function is uncertain. Measurement of TC II-bound B12 (holo-TC II or holo-TC) would be expected to provide a more reliable measure of B12 availability to

tissues than total serum B12. With the initial assay methods, holo-TC II appeared to be influenced by factors other than B12 status and its specificity for B12 deficiency was low.8 Studies with the new radio-immunoassays have shown that holo-TC II is slightly more sensitive than serum B12 in detecting individuals with high MMA and tHCYS levels [48]. However, they have provided conflicting data on specificity and further studies are required before the value of holo-TC II in determining B12 status is established [49 – 52] in one study the specificity was found to be 89%.In a recent investigation, Chen et al [53] found that deficiency of B12 was much more important than impaired B12 absorption in determining holo-TC II levels. There was a considerable overlap between serum holo-TC II levels of treated patients with pernicious anaemia and control subjects indicating that contrary to previous suggestions holo-TC II levels cannot be used as a surrogate for the Schilling test.

Deoxyuridine suppression test [DUST]

This test gives a measure of the efficiency with which marrow cells methylate de-oxyuridylate to thymidylate and is abnormal in both B12 and folate deficiency [54-57]. Worldwide, it is only performed in a very few laboratories. The DUST is more sensitive in detecting B12 deficiency than MMA or tHCYS levels [57] but has the disadvantage that it has to be done on bone marrow cells.

Biochemical test for assessing folate status

Serum and red cell folate

Serum or red cell folate assays or both are the initial tests used for the assessment of folate status. Most of the folate in serum is in the form of 5-methyltetrahydrofolate monoglutamate and that in red cells in the form of various polyglutamates. The red cell folate level is a measure of folate status over the preceding three months (i.e. over one red cell lifespan). It is generally considered that the serum folate level mainly reflects current and recent folate intake and, consequently, is more useful in detecting acute folate deficiency than long-term deficiency[58]. On the basis of highly significant statistical correlations between serum folate and red cell folate measured by microbiological and fully-automated methods [59, 60]. Some have suggested that the serum and red cell folate assays give similar information. Though statistically significant, the correlations are weak and the regression coefficients of 0.55 found by Jaffe & Schilling [60] and 0.49 found by Phekoo et al [59] indicate that only 30% 39 and 24% respectively of the variation of the serum folate can be accounted for by variations of red cell folate.

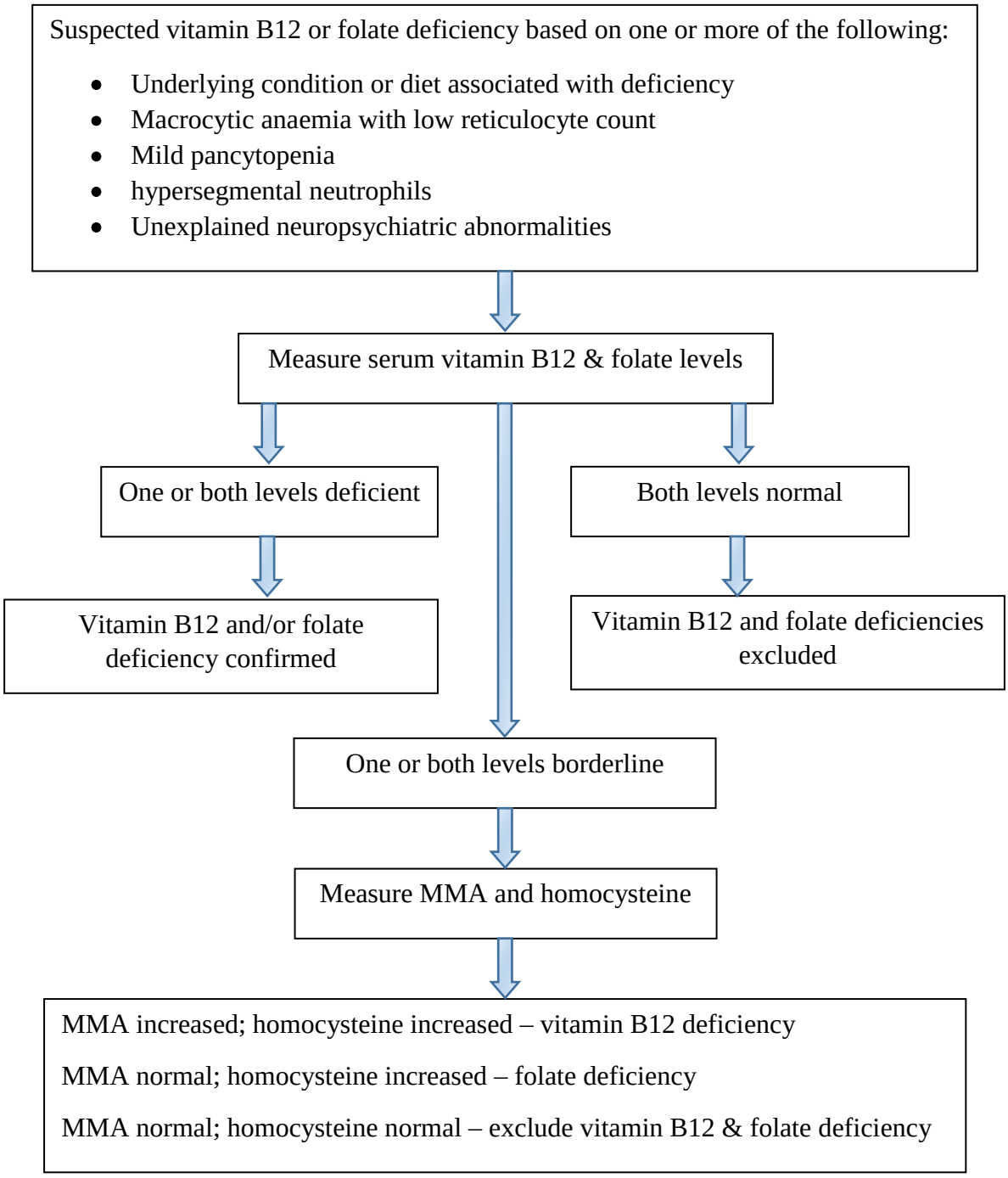
The accuracy of folate assays and particularly of fully-automated red cell folate assays is questionable. The results obtained depend on the assay method - microbiological, radioassay, fully-automated or GC-MS [61, 62]. This may arise from differences in the method of preparation of the haemolysate and in the completeness of the deconjugation of folate polyglutamates to monoglutamates. There are also difficulties in assay design resulting from the fact that the red cell-derived monoglutamates do not consist of one species of folate molecule but a mixture of folates.

The specificity of a low red cell folate in the diagnosis of folate deficiency is poor largely because upto 60% of B12-deficient patients have low red cell folate levels. By contrast, serum folate levels are increased in 20% and low in only 10% of such patients. In practice, folate deficiency is assumed if a low folate level is found together with a normal B12 level. If the B12 level is also low, it is important to consider the possibility that the primary deficiency is of B12 rather than folate by considering the clinical setting, measuring MMA levels (if possible) or by performing a Schilling test.

Not all patients with a low red cell folate level have metabolic evidence of folate or/and B12 deficiency. In one study with a radioassay, low red cell folate levels were found in 8 of 45 macrocytic patients who gave normal DUST results [63].

Plasma total homocysteine (tHCYS) and serum/plasma methylmalonic acid (MMA) as mentioned earlier, tHCYS is elevated in both folate and B12 deficiency. The increased tHCYS levels in folate deficiency return to normal after treatment with folate but not with B12 [64] MMA levels are normal in folate deficiency.

Algorithm for diagnostic testing for suspected vitamin B12 or folate deficiency



Treatment

The urgency of correction:

Most of the people with vitamin B12 or folate deficiency present asymptomatically with an incidental laboratory finding or with the slow development of symptoms. Repletion of the deficient vitamin can be instituted over a period of weeks in these instances. However, in certain cases it may be intervene more urgently:

- Symptomatic anaemia or neurologic or neuropsychiatric findings, due to the risk of adverse events and irreversibility of neurologic deficits
- Pregnancy, as the developing fetus may be affected
- Neonates and infants, whose development may be impacted

However, there is no evidence of benefit from using a higher dose. In extremely rare cases of severe deficiency with hemodynamic compromise due to severe anaemia, blood transfusion may be given [65, 66]. Vitamin B12 and/orfolic acidshould also be administered as appropriate, but these cannot be relied on for emergency therapy because improvements in red blood cell production take several days to take effect.

Available therapeutic preparations:

- Vitamin B12 (also called cobalamin) is available as cyanocobalamin, which contains a cyanide (CN) atom introduced during chemical synthesis and hydroxocobalamin. Cyanocobalamin is predominantly used in the United States

and hydroxocobalamin is predominantly used in Europe; both are effective in treating vitamin B12 deficiency [67]. Of note, maintenance doses of cyanocobalamin are administered monthly; maintenance hydroxocobalamin is administered less frequently (once every two to three months) [65, 66].

- Folic acid is also called vitamin B9. Folinic acid (also called leucovorin) is a naturally occurring form of reduced folate that is primarily used to prevent toxicities of methotrexate; while more expensive, it is effective for treating folate deficiency.

Adverse effects/overdose:

Vitamin B12 and folate are water-soluble vitamins that are excreted when stores are adequate. Rare cases of hypersensitivity or acneiform eruptions with vitamin B12 have been reported [65, 66]. Reports of serious adverse effects from administration or intake of greater-than-recommended doses have not been observed

Prevention of vitamin B12 deficiency:

Specific interventions to prevent vitamin B12 deficiency are unnecessary in the vast majority of individuals who consume a normal diet. However, certain settings are associated with an increased risk of deficiency

- Vegan or vegetarian diet
- Gastric or bariatric surgery

- Disorders of the small intestine
- Neonates born to vitamin B12-deficient mothers
- Nitrous oxide exposure

Cobalamine deficiency:

Apart from specific therapy related to the underlying disorder, the mainstay of treatment for cobalamine deficiency is replacement therapy. Parental treatment begins with 1000 micro g cobalamine daily for 1 week followed by weekly for eight weeks and every month later for the rest of patient's life.

Folate deficiency:

As for cobalamine deficiency, folate deficiency is treated by replacement therapy. The usual dose of folate is 1 mg/d by mouth, but higher doses (upto 5 mg/d) may be required for folate deficiency due to malabsorption.

Tropical sprue [68]

Tropical sprue is a clinical syndrome with unknown aetiology typically characterized by an acquired chronic diarrheal illness, small bowel mucosal abnormalities & malabsorbtion resulting in nutritional deficiency and weight loss. The 1st description of tropical sprue termed idiopathic malabsorption of the tropics was attributed to dr.william Hillary who studied individuals with chronic diarrhoea in Barbados in 1759. Baker, in 1974, broadly defined tropical sprue as malabsorption of two or more substances in

people in the tropics when other causes have been excluded. Klepstein's definition – chronic small bowel diarrhoea with malabsorption of two unrelated substances [carbbohydrates & fatty acids], abnormal small intestine histology, exclusion of other causes of malabsorption and persistent response to treatment.

Epidemiology – affects residents, expatriates and tourists of tropical region including southeast - Asia, the Indian subcontinent, west Africa, central America, south America, the Caribbean, and Puerto rico. India in 2011, dutta et al. estimated the prevalence of tropical sprue to be high as 29% in southern Indians diagnosed with malabsorptive syndrome.

Aetiology

- Exact causative agent still unknown
- The disease may start acutely or several months after an episode of gastrointestinal infection. This initial insult is thought to cause intestinal stasis leading to small intestinal bacterial overgrowth and enterocyte injury & dysfunction.
- Environmental factor, diet, and genetics.

Pathophysiology:

- Slowing of small bowel transit time by many mechanism
- Peptide YY, enteroglucagon, neurotensin, and glucagon like peptide – 1 and stasis of fat [ileal brake] are causing enterocyte damage

Clinical manifestation:

- Chronic profuse diarrhoea, weight loss, statorrhea, bloating, campy abdominal pain, anorexia and weakness
- Nutrient deficiency – folate, vitamin B12, lipid soluble vitamins [A, D, E, K], hypoproteinemia, hypomagnesemia and hypophosphatemia
- Iron deficiency anaemia rare in tropical sprue

Diagnosis:

Diagnosis of exclusion – exclude other causes of chronic diarrhoea

- Quantitative stool fat estimation
- D – xylose testing
- UGI scopy and deep duodenal biopsy

Differential diagnosis:

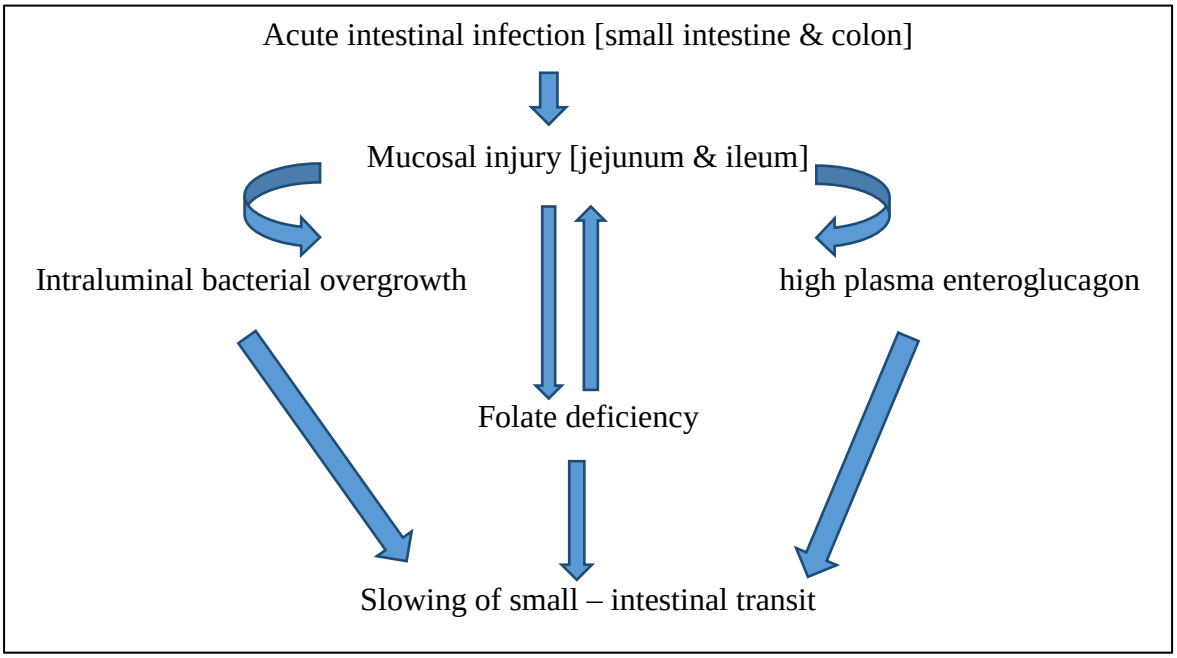
Celiac disease, lactase deficiency, inflammatory bowel disease, small intestinal bacterial over growth, tropical pancreatitis, intestinal scleroderma, amyloidosis, lymphoma, HIV, mycobacterim tuberculosis, strongyloides stercoralis, giardia intestinalis, entamoeba histolytica, cryptosporidium parvum, cyclospora cayetanesia and isosopora belli.

Treatment

Folic acid supplementation 5-10mg/day for 6 months, though longer duration of therapy may be necessary. Folic acid supplementation alone fast recovery and reverse blunting villous.

Those who not responding to folic acid alone, then add tetracycline 250mg four timesa day or doxycycline 100mg twice a day for 3-6 months. Response to treatment can take weeks to months.

Figure – 4: possiable mechanism of tropical sprue



Hypersplenism [69]

Hypersplenism refers to a group of syndromes that involve splenomegaly and peripheral cytopenia of various causes. [Enlarged spleen which causes rapid and premature destruction of blood cells]

Classification:

1. Primary hypersplenism
2. Secondary hypersplenism
3. Occult hypersplenism

Primary hypersplenism -The cause is not clear

Primary splenic hypersplenism:

- Non – tropical idiopathic splenomegaly
- Primary splenic granulocytopenia
- Primary splenic pancytopenia
- Splenic anaemia or thrombocytopenia

Secondary hypersplenism:

Infections

Viral hepatitis, brucellosis, subacute or chronic diseases, infectious mononucleosis syndrome and malaria

Alcohol use such as long-term or excessive drinking

Portal hypertension (PH), such as liver cirrhosis of various causes including post-hepatitic: cirrhosis, alcoholic cirrhosis, and biliary cirrhosis, fatty liver cirrhosis, post-hepatitic autoimmune cirrhosis, schistosomiasis-induced cirrhosis, and drug-induced cirrhosis, as well as hemosiderosis and portal vein thrombosis

Granulomatous inflammation

Systemic lupus erythematosus, rheumatoid arthritis, chronic syphilis, chronic tuberculosis, felty's syndrome, and sarcoidosis

Malignancies

Splenic lymphosarcoma, leukemia, and cancer metastasis

Chronic hemolytic diseases

Hereditary spherocytosis, autoimmune hemolytic anaemia, and thalassemia

Lipidosis

Gaucher's disease, and Niemann-Pick disease

Myeloproliferative disorders

Polycythemia vera, chronic myeloid leukemia, and myelofibrosis

Other diseases - hemophagocytic syndrome (HPS), relatively benign hamartoma, splenic cyst, splenic artery aneurysm, and cavernous hemangioma.

The most common hypersplenism is secondary to post-viral hepatitis, cirrhotic PH.

Occult hypersplenism:

Both primary & secondary hypersplenism, if the underlying cause is not serious, together with benign bone marrow hyperplasia and sufficient bone marrow compensation, peripheral cytopenias may not occur. In this case, hypersplenism becomes occult with no symptoms.

However, once the bone marrow hematopoietic function is suppressed by factors such as infection or drugs, monolineage or multilineage peripheral cytopeniaoccurs, accompanied by clinical symptoms, which is not classified as occult hypersplenism.

Pathogenesis:

The exact pathogenesis of hypersplenism induced peripheral cytopenia is still inconclusive, several mechanism has been identified.

Retention in the spleen

In portal hypertension, the spleen can increase 8 – 10 times its normal size [hyperemic splenomegaly], as consequence, there is retension of large number of WBC, RBC, and platelets in the spleen. Number of retained blood cells can be 5.5 – 20 times higher than the normal level, thus facilitating capture, phagocytosis or destruction of blood cells by phagocytes resulting in peripheral cytopenias.

In 1965, aster found by using ^{51}Cr-labeled platelets that under normal circumstances, approximately one – third of platelets are stored in the spleen, and the remaining two third in the blood circulation.

In hypersplenism, 50 – 90% of platelets are retained in the enlarged spleen resulting in a reduction of platelets in the circulating blood.

Diagnostic criteria of hypersplenism

1. Anaemia, leukopenia or thrombocytopenia, either singly or in combination
2. Cellular or hyperplastic bone marrow
3. Splenomegaly
4. Significant improvement in the peripheral blood picture following splenectomy

Treatment

- Non - surgical treatment
- Treat etiological cause and treat concomitant disease process

Etiological treatment

Hypersplenism has many causes, and treatment should direct specific causes.

Kalambokis and tsianos [70] observed an increased incidence of peripheral cytopenia in liver cirrhosis patients, this related to hypersplenism, and activation inflammatory mediators, by endotoxin produced by intestinal bacteria. In this situation should be prescribed for antibiotics to counteract endotoxemia in patients with cirrhosis to increase blood cell count.

Zucchini et al [71] fount that electromagnetic hyperthermia was effectively treating thrombocytopenia in a rat model cirrhotic hypersplenism.

Chernykh et al [72] report satisfactory outcomes achieved by autologous stem cell transplantation in the treatment of peripheral cytopenias due to cirrhotic portal hypertension.

Zhang et al [73] proposed that phosphatidylinositol 3-kinase regulatory subunit 1 [PIK3R1] may play an important role in the pathogenesis of portal hypertension and regulating the inhibition of macrophage activity, and that inhibition of PIK3R1 expression may potentially be useful for the treatment of portal hypertension and hypersplenism

External irradiation & ablation

Kenawi et al treated eight patient with liver cirrhosis, splenomegaly and hypersplenism by externally irradiating the spleens using radioactive co – 60. Laboratory data showed that the hemogram returned to completely normal in two patients and partially normal in three patients. Moreover, remission of chronic splenic pain was obtained in all patient and no significant complications were reported [40]. Ismail et al [69] also observed increased platelet counts & improved splenic pain in patients treated with splenic irradiation. Feng et al [69] treated patient with hypersplenism using radiofrequency ablation which give effective symptoms relief while maintaining normal blood Tuftsin levels essential for the anti – infective and antitumor functions of the body.

Partial splenic artery embolization

In 1979, spigos et al used partial splenic artery embolization for the first time to treat hypersplenic patients with success [74]. Thereafter, it has been applied in the treatment of portal hypertension, hypersplenism, and bleeding esophagogastric varices [75]. This procedure not only increases platelet & leukocyte count [38], but also reduces splenic size, improves pancytopenia [72], and stimulates the immune system [76]. Despite some clinical success in treating splenomegaly and hypersplenism, the indications for partial splenic artery embolization are limited due to serious complications, such as splenic infarction and abscess, which could result in a high risk of death (77).

Total splenectomy

Liver transplantation

While liver transplantation for the treatment of hypersplenism has not been reported, hypersplenism is often developed from liver cirrhosis. Severe cirrhosis is often associated with serious hypersplenism.Liver transplantation may reduce the splenic size and the portal pressure, decrease the risk factors of bleeding, and eventually eliminate hyper-splenism (78).

Absolute indications for splenectomy [79]

Splenic trauma, splenic rupture, splenic abscess (e.g. tuberculous infection), splenic cysts, neoplasm, aneurysm of splenic artery.

Table – 7: Relative indication of splenectomy

1. Blood and reticuloendothelial disease a) **Haemolytic** i. Congenital haemolytic anaemia ii. Acquired haemolytic anaemia iii. Thalassaemia b) **Haematological malignancy** i. Acute leukemia ii. Chronic myeloid leukemia iii. Chronic lymphatic leukemia iv. Lymphoma (Hodgkin's) c) **Myeloproliferative disorders** i. Polycythaemia vera ii. Myeloid metaplasia (myelofibrosis) d) **Thrombocytopaenic disorders** i. Acute ITP ii. Chronic ITP	**2. Infective and inflammatory** a) Parasites (hydatid) b) Protozoal (malaria) c) Inflammatory (Felty's syndrome)
3. Neoplastic a) Angioma b) Cysts c) Metastases	**4. Cryptogenic** a) Tropical splenomegaly b) Non-tropical splenomegaly

5. Congestive a) Portal hypertension i. Intrahepatic ii. Extrahepatic	**6. Metabolic storage disorders** a) Amyloidosis b) Gaucher's disease

Complication of splenectomy

- Haemorrhage
- Pulmonary atelectasis and pneumonia
- Sympathetic pleural effusion
- Subphrenic abscess/cellulitis
- Gastric ileus
- Acute pancreatitis
- Severe thrombosis after splenectomy for myeloproliferative disorders

Aplastic anaemia

Aplastic anaemia is defined as pancytopenia with hypocellular bone marrow in the absence of an abnormal infiltrate and with no increase in reticulin [80]. Aplastic anaemia is a heterogenous group of disorder that result in pancytopenia and hypocellular bone marrow.

Stem cell failure mechanism

Aplastic anaemia is a specific disease entity reflecting a deficiency of haematopoietic stem cells, resulting in peripheral pancytopenia and bone marrow aplasia. In contrast, bone marrow failure is a more encompassing term that describes pancytopenia from a variety of different mechanisms. Examples include bone marrow replacement by tumor or fibrosis, and myelodysplasia, in which the stem cells are malignant, may be present in increased numbers, but do not mature normally.

Stem cell failure can be congenital or much more often, acquired. The major causes of acquired aplastic anaemia are exposure to wide variety of chemicals and drugs, ionizing radiation, and some viruses. It may rarely complicate orthotopic liver transplantation; aplastic anaemia in this setting has a very poor outcome except in those patient who develop the disorder in the context of fulminant hepatic failure [81]

Aplastic anaemia has also occurred in patient with other immune disorder & occasionally in pregnancy [82, 83]. The aplasia associated with pregnancy is frequently self-limited, ending with delivery.

Idiopathic aplastic anaemia

The causes remains obscure in most patients with acquired aplastic anaemia. Several observations are consistent with destruction or suppression of the stem cell by autoimmune mechanism [84, 85]

- Many of these patients respond to immunosuppressive therapy

- There is an association of aplastic anaemia with the rare immunologic disease eosinophilic fasciitis

- Aplasia can occur in the context of graft-versus-host disease following allogenic hematopoietic cell transplantation

- Bone marrow lymphocytes of patients with aplastic anaemia can inhibit hematopoiesis when cultured with patient or normal marrow

- Oligoclonal or monoclonal expansions of CD8+ T cells have been found in patients with idiopathic aplasia anaemia, as well as in the closely releated disorder paroxysmal nocturnal hemoglobinuria

- In a small study, T-cell receptor zeta chain expression was decrease in the majority of patients with aplastic anaemia, comparable to that seen in other autoimmune diseases; expression was decreased regardless of disease activity or treatment status

Most cases are idiopathic, presumably an autoimmune disorder. Some acquired aplastic anaemia cases are associated with bone marrow toxicity from chemical & physical agents, viral infections, mycobacterial infections, & other causes. Rarely, several inherited bone marrow failure syndromes have aplastic anaemia as a key pathological component. Family member of these patients should be screened. Screening of family member should also be offered to 10% of aplastic anaemia patient with spontaneous

mutation or haploinsufficiency of telomerase. The condition present with skin pallor, ecchymosis, petechiae, and possible fever.

Aplastic anaemia various causes

- **Idiopathic; presumed autoimmune [70-80%]**
- **Ionizing radiation**
- **Viral infections**

  Epstein – barr virus

  HIV

  Dengue

  Hepatitis virus

  Parvovirus
- **Chemical exposure, including cytotoxic agents**

  Benzene

  Sulphur or nitrogen mustard and congeners

  Anti metabolites

  Anti mitotic agents

  Inorganic arsenic

  Dichlorovinylcysteine

  Insecticides

- **Medications**

  Anti microbial agents – chloramphenicol, organic aresenicals, qquinacrine, penicillamine

  Anti convulsant – acetazolamide, carbamazepine, hydantoins, trimetadione

  Anti thyroid drugs

  Anti diabetic drugs

  Estrogens

  Anti histamines

  Analgesics

  Sedatives & tranquilizers

  Gold compounds

- **Associated**

  Inherited bone marrow failure syndrome [eg – fanconi anaemia, dyskeratosis congenital, shwachman-diamond syndrome, congenital amegakaryocytic thrombocytopenia]

  Paroxysmal nocturnal hemoglobinuria

  Myelodysplastic syndrome

  Acute myelogenous leukemia

Investigations:

- Complete blood count and reticulocyte count**,** blood film examination**,** HbF% in children**,** bone marrow aspirate and trephine biopsy, including cytogenetics**,** peripheral blood chromosomal breakage analysis to excludeFanconi anaemia if <50 years**,** flow cytometry for GPI-anchored proteins (see note belowconcerning Ham test)***,** urine haemosiderin if ham test positive or GPI-anchored proteindeficiency**,** vitamin B12 and folate**,** anti-nuclear antibody and anti-dsDNA**,** peripheral blood gene mutation analysis for dyskeratosis congenital DKC1, TERC, ?TERT) if clinical features or lack of response toimmunosuppressive therapy.

Severity of aplastic anaemia [86]:

1. Severe aplastic anaemia [camitta et al, 1975] – bone marrow cellularity <25%, or 25 -50% with residual haemopoietic cells*

   2/3rd of the following:

   - Neutrophil count 0.5 x 10^9 /l
   - Platelet count <20 x 10^9 /l
   - Reticulocyte count <20 x 10^9 /l

2. Very severe aplastic anaemia [bacigalupo et al 1988] – as for severe aplastic anaemia but neutrophil count <0.2 x 10^9 /l

3. Non – severe aplastic anaemia – patient not fulfilling criteria for very severe and severe aplastic anaemia

*Cellularity should be determined by comparison with normal controls

(Tuzuner & Bennett, 1994)

Table – 8: Differential diagnosis of pancytopenia and a hypocellular bone marrow

- Hypocellular MDS/acute myeloid leukemia
- Hypocellular acute lymphoblastic leukemia
- Hairy cell leukemia
- Lymphoma
- Mycobacterial infection – commonly in atypical organisms
- Anorexia nervosa or prolonged starvation

Treatment

Supportive care, including antimicrobials, erythrocyte & platelet transfusion, bone marrow transplantation, and immunosuppressive therapy. Use of offending drugs or agents that appear to be causing the marrow failure must be discontinued. In the past, the diagnosis of aplastic anaemia was associated with a 67% mortality, most commonly a consequence of infection resulting from neutropenia or bleeding resulting from thrombocytopenia.

Aplastic anaemia should be considered in all patients with pancytopenia. Common causes of anaemia [eg – iron deficiency, folate/B12 deficiency, alcoholism, acute sepsis, or marked inflammatory condition flares] should be ruled out before proceeding to a bone marrow biopsy. Definitive diagnosis is based on a bone marrow biopsy showing hypocellularity without another diagnosis to account for the hypocellular condition. Normal cytogenetics or no chromosomal abnormalities are the most common findings. Finding unbalanced lesions common to myelodysplastic syndrome suggest either a possible disease transformation from aplastic anaemia to myelodysplastic syndrome, or a primary diagnosis of hypocellular myelodysplastic syndrome. From a practical perspective, the critical issue is to distinguish severe and very severe aplastic anaemia, which usually require treatment, from moderate aplastic anaemia, which usually requires only monitoring & supportive care.

Bone marrow transplantation vs immunosuppressive therapy in aplastic anaemia

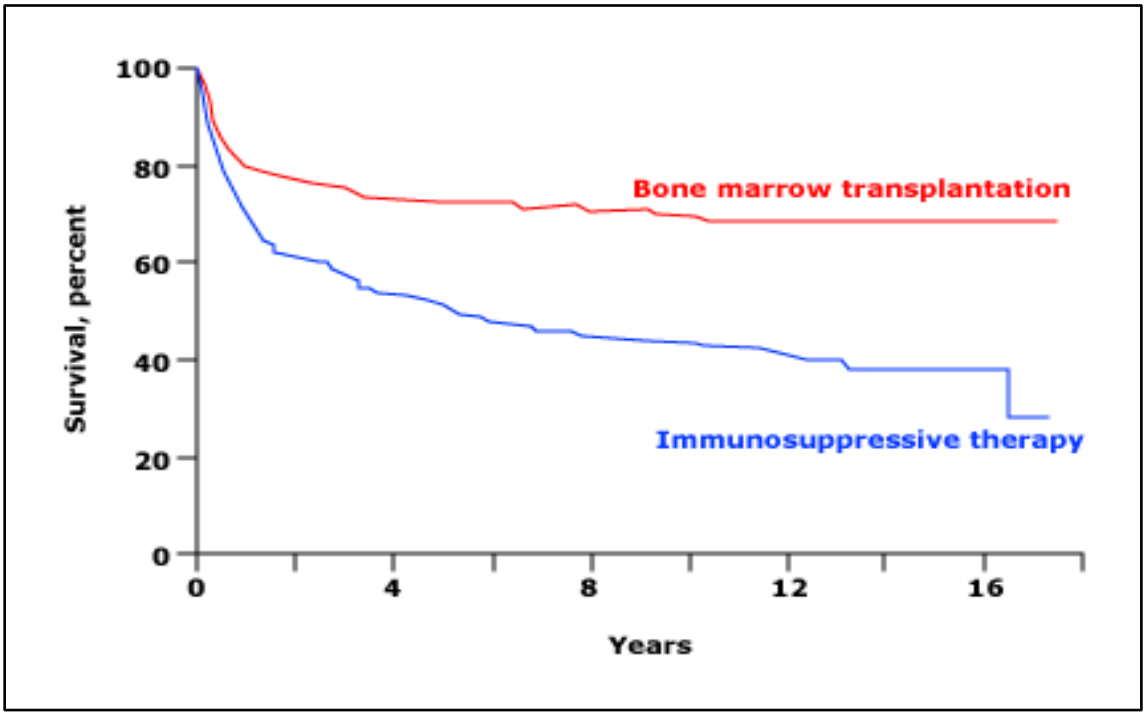


Figure – 4: The above graph shows the data obtained from the study conducted by Doney.k et al it shows the survival was better in the group of 168 aplastic anaemia patients who underwent bone marrow transplant therapy when compared to the group of 227 aplastic anaemia patients who underwent immunosuppersive therapy [87].

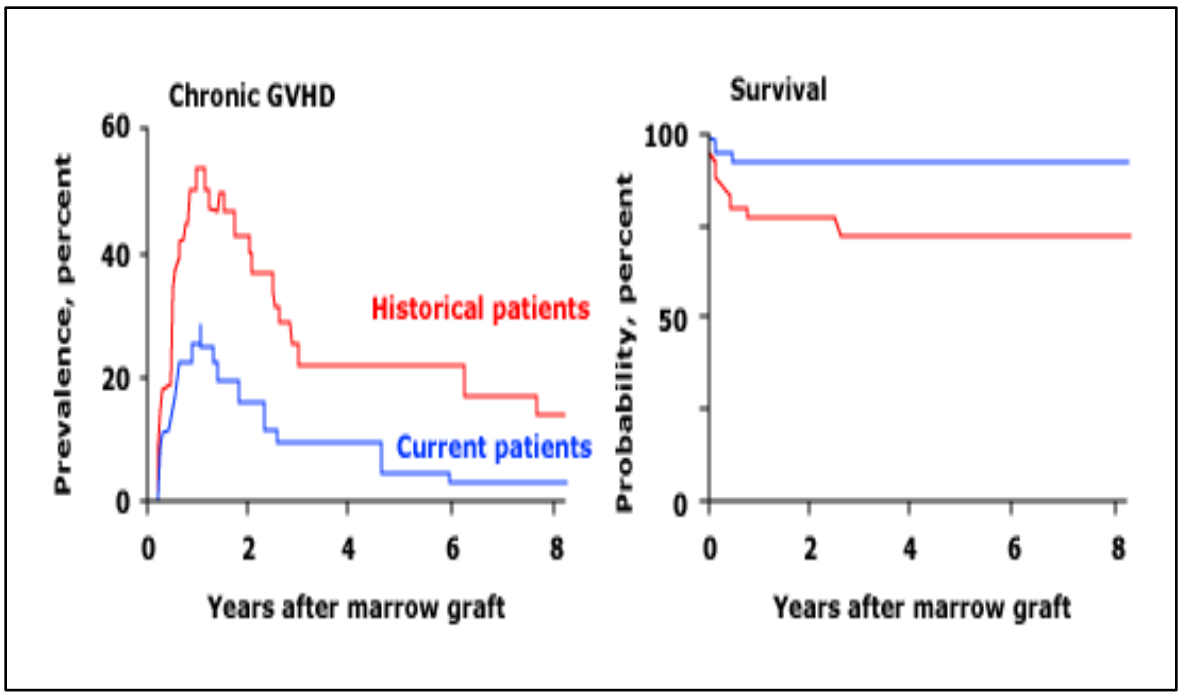


Figure – 5: The above graph from the data obtained in the study conducted by Storb.r et al shows that the incidence of graft versus host disease was less in group of patients who were conditioned with antithymocyte globulin prior to bone marrow transplantation, similarly the survival was better in the above mentioned group compare to bone marrow transplantation patients who were conditioned with cyclophosphamide alone [88].

RESULTS

The total population was 50[n]. The various aetiologies of pancytopenia identified by this study population. Most common aetiology is megaloblastic anaemia accounting for 50%. Second most common causes was haematological malignancies accounted for 16%. Followed by decreasing trend – hypersplenism 10%, aplastic anaemia 8%, dengue fever with pre-existing iron deficiency anaemia 8%, systemic lupus erythematosus 4%, hemophagocytic lymphohistocytosis 4%.

figure - 6: distribution of various causes in pancytopenia

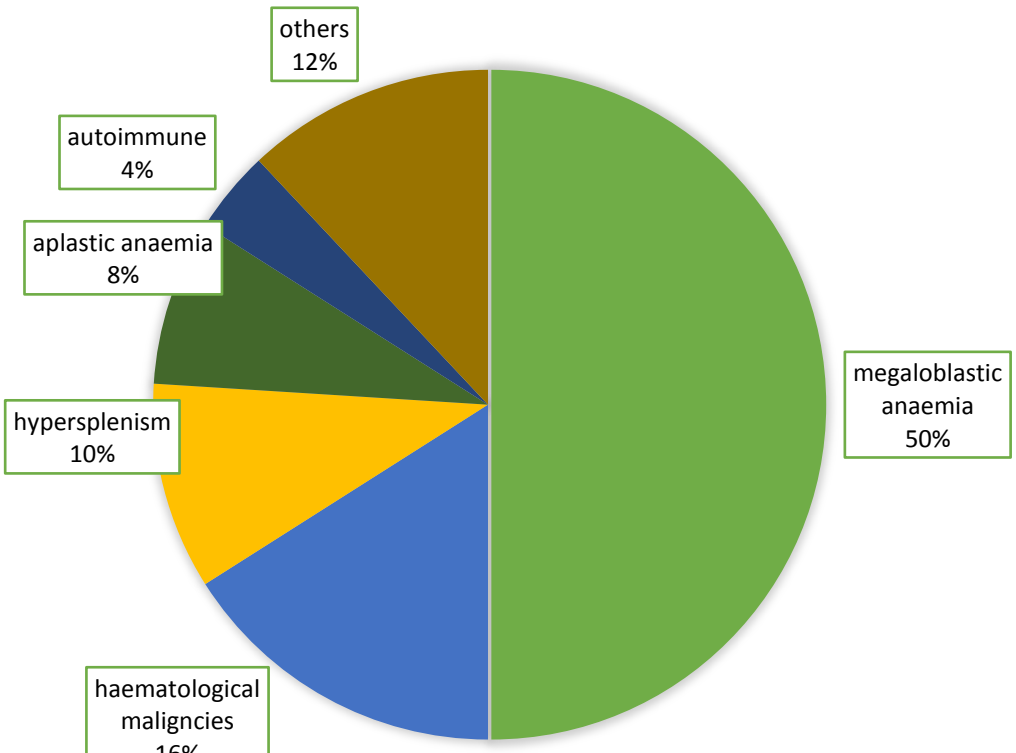
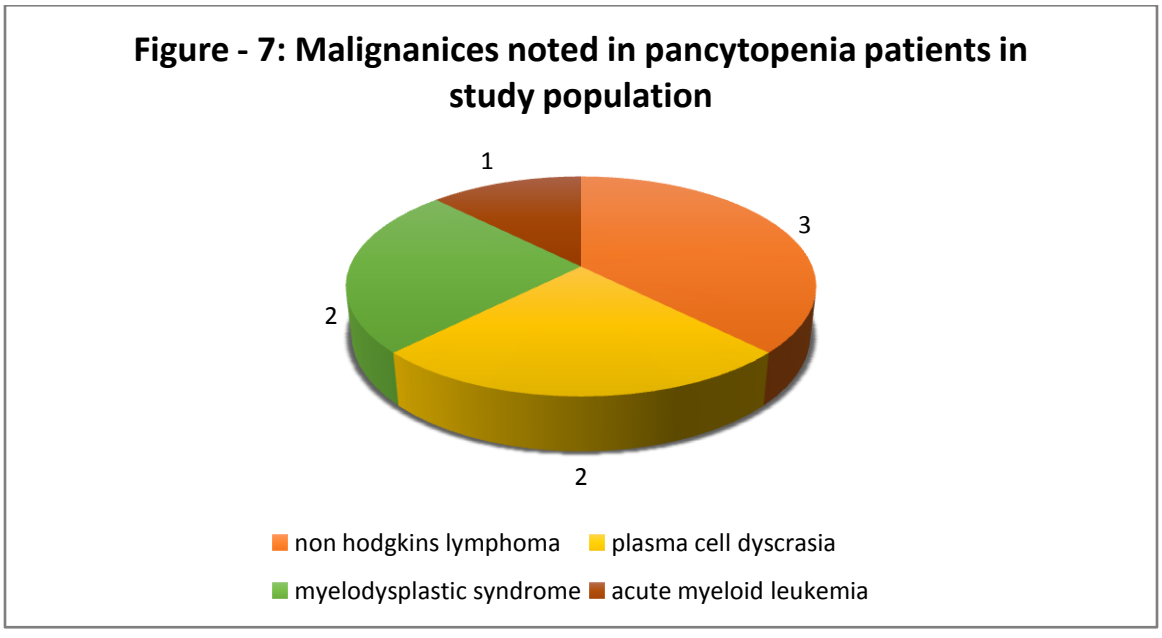


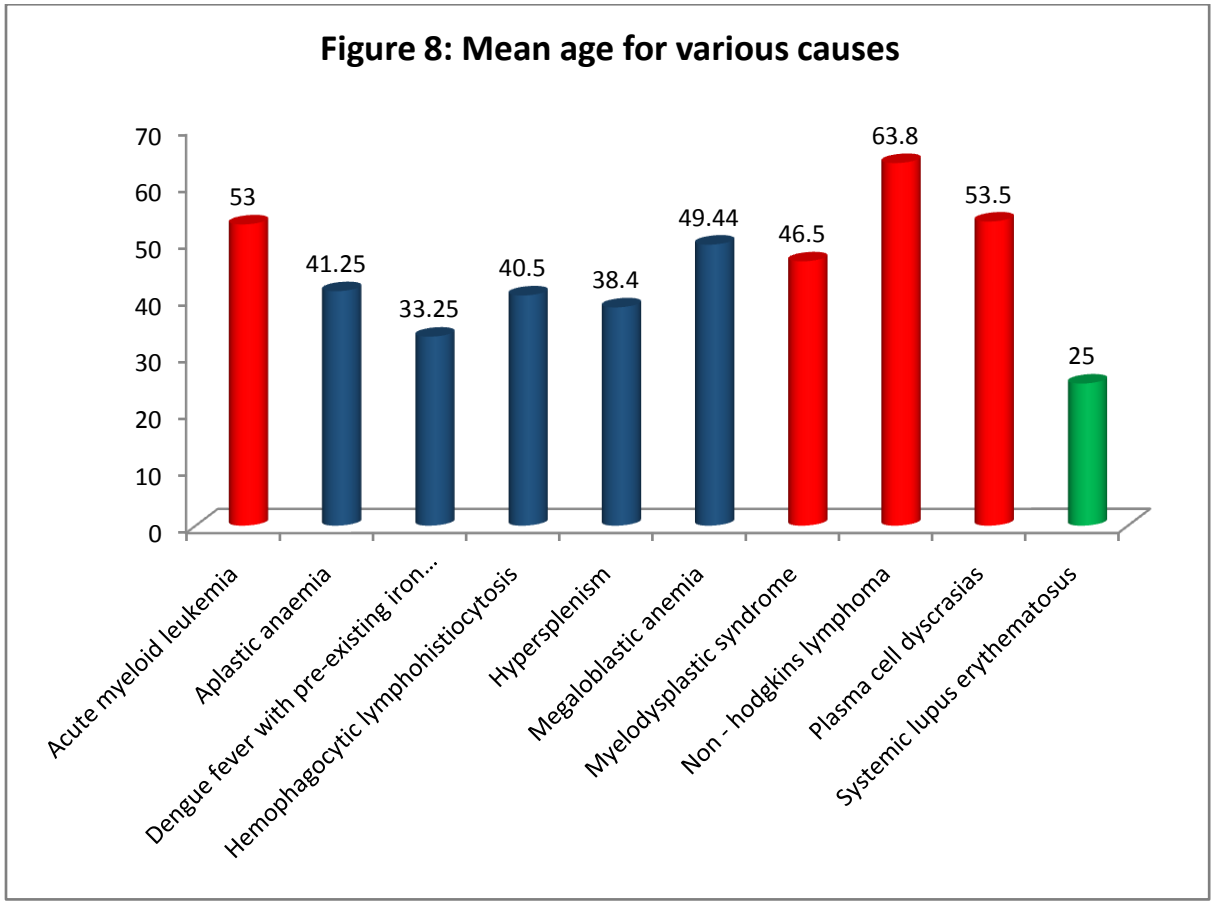
Table – 9: Showing causes, no of patients and percentage in pancytopenia patients

Causes	No of patients	Percent
Megaloblastic anaemia	25	50.0
Hypersplenism	5	10.0
aplastic anaemia	4	8.0
Dengue fever with pre-existing iron deficiency anaemia	4	8.0
systemic lupus erythematosus	2	4.0
plasma cell dyscrasia	2	4.0
myelodysplastic syndrome	2	4.0
Hemophagocytic lymphohistiocytosis	2	4.0
acute myeloid leukemia	1	2.0
Non - hodgkins lymphoma	3	6.0
Total	**50**	100.0

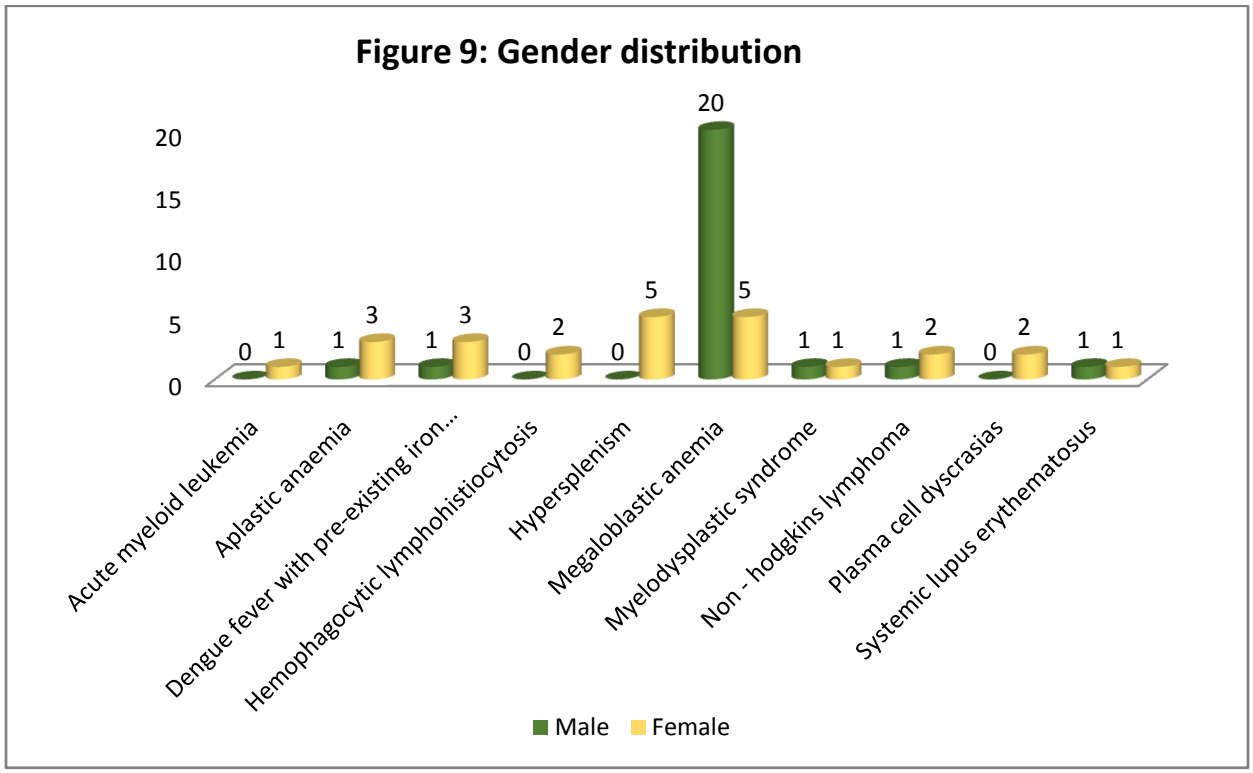
The incidence of malignancies in study population is 16%. The malignancies that were present in the study population were as follows.



The mean age of the study population is represented in the following figure. Mean age of patients with SLE was noted to be lower when compared to others as expected. Malignancies [red bar] were noted to have a higher mean when compared to all cause mean age.



Gender distribution of various causes – megaloblastic anaemia & malignancies were more common in males than females.



Age wise distribution in pancytopenia patients, more common age group fall under 41-50yrs & 61-70yrs.

The mean of various laboratory parameters are considered below in following table. **Table – 10:** Represents the mean, standard deviation, range of various parameters, haemoglobin, WBC, platelets, MCV, RDW, MPV [minimum to maximum].

Mean total WBC – 2.54±0.99

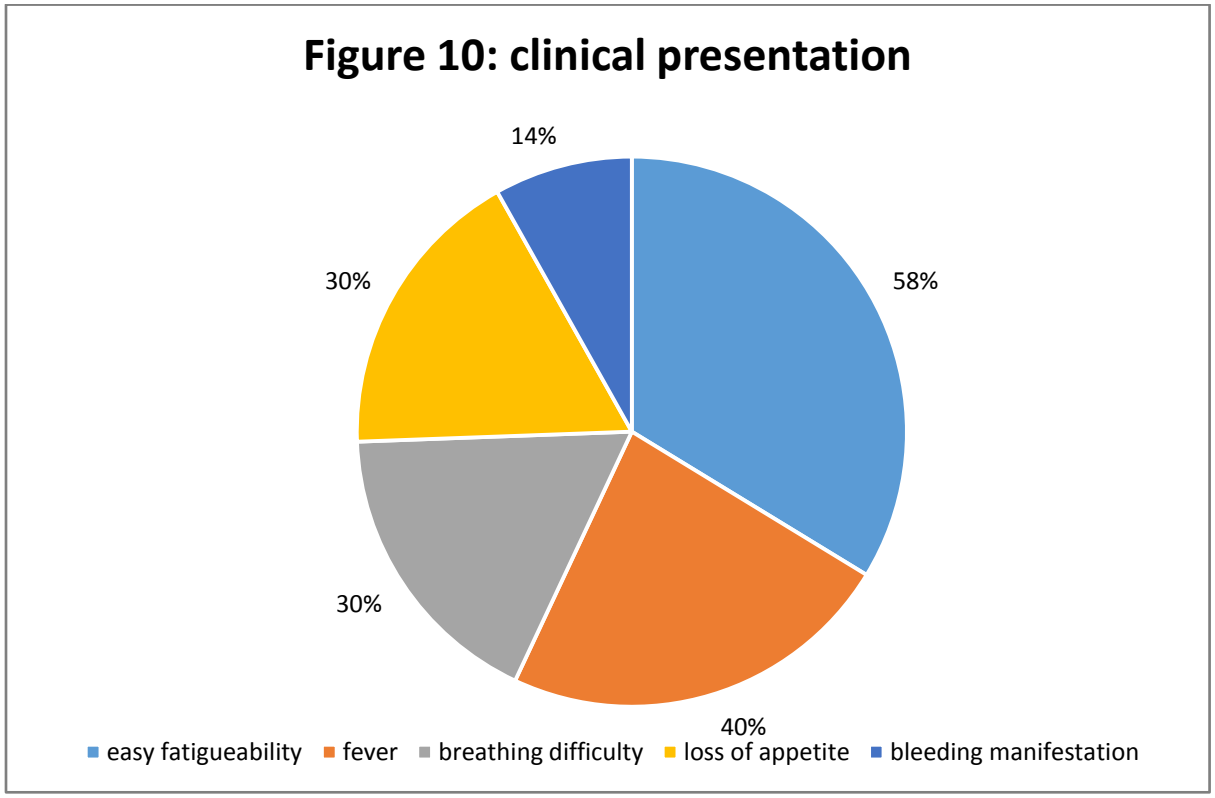
Mean haemoglobin – 5.8±2.1

Mean platelet – 49.12±31.75

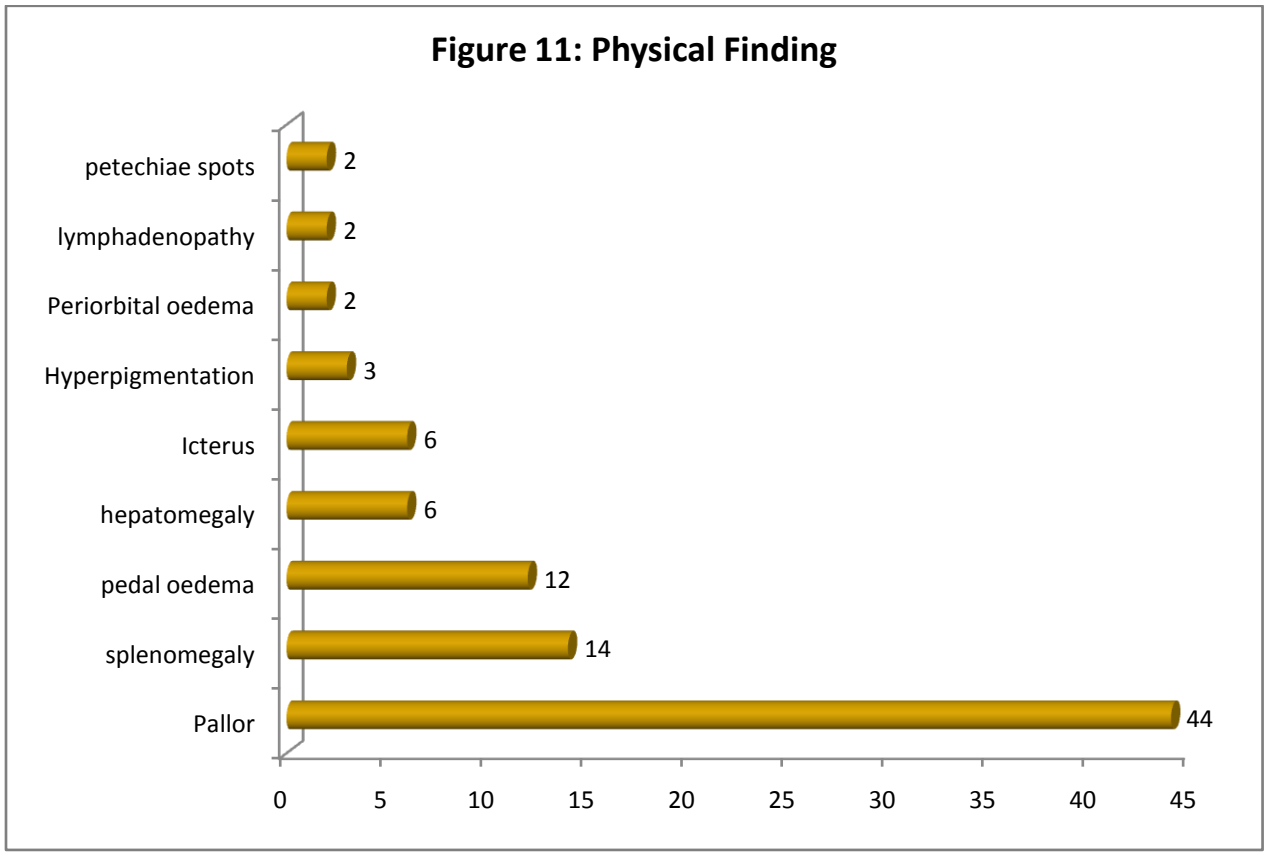
	Minimum	**Maximum**	**Mean**	**Std. Deviation**
HB	2.00	10.00	5.8140	2.10994
WBC	.40	3.90	2.5420	.99757
Platelet	3.00	99.00	49.1200	31.75650
MCV	54.00	133.00	93.6980	20.22669
RDW	17.10	42.00	28.4083	8.09788
MPV	8.00	11.60	9.3417	.99909

Clinical features:

The most common presenting complaints of patients presenting with pancytopenia was easy fatigability 58%, fever – 40%, breathing difficulty & loss of appetite – 30%. Bleeding manifestation was the presenting complaint in only 14%.

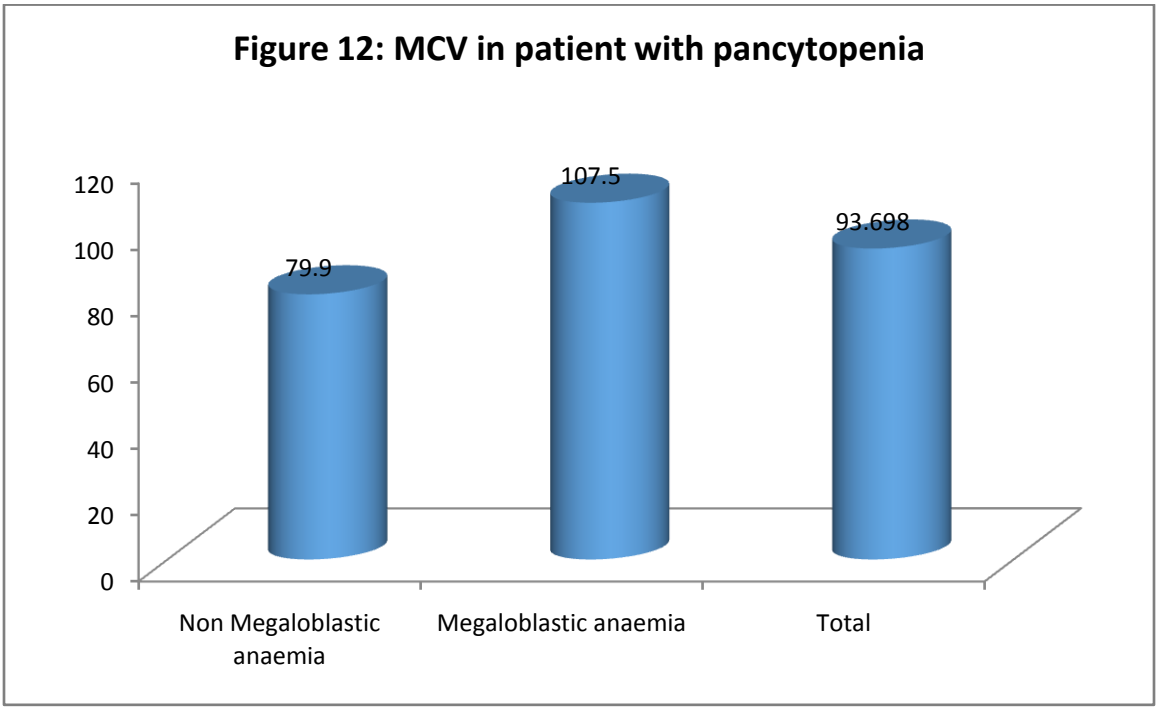


Physical examination – most common physical finding in our study group; pallor 88%, splenomegaly 28%, pedal oedema 24%.



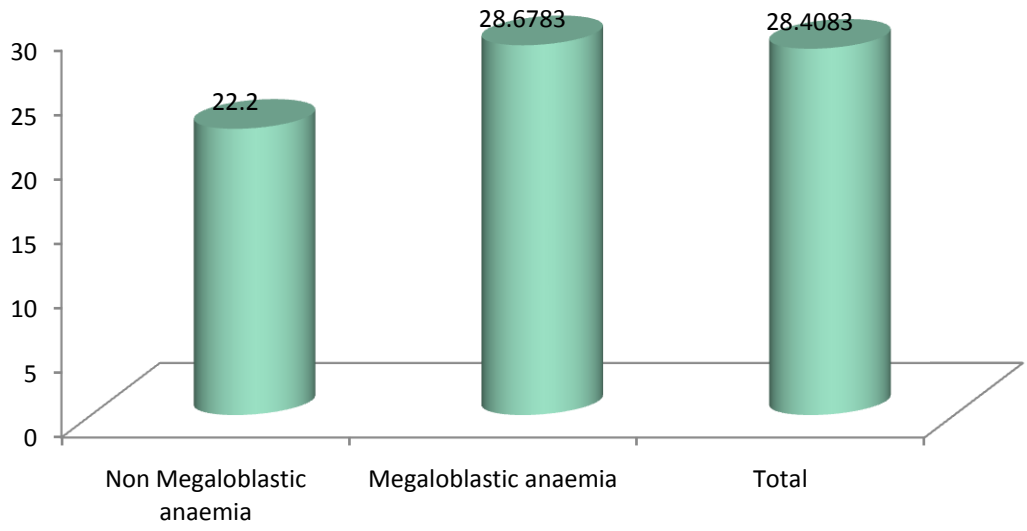
The MCV of megaloblastic anaemia when compare with patient with non megaloblastic causes of pancytopenia and all cause MCV is shown in figure.

The mean MCV of patients with megaloblastic anaemia is 107.5 which is much higher than the non megaloblastic anaemia which is 79.9.

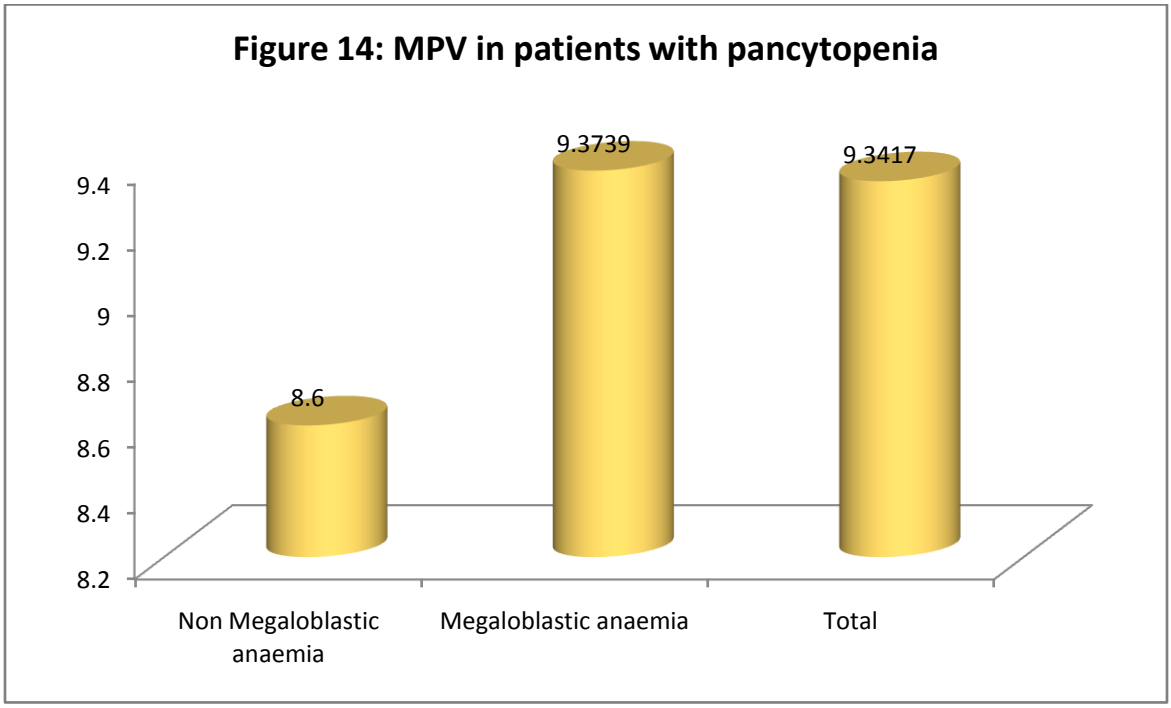


This figure represent RDW in various causes of pancytopenia. The RDW in patient with megaloblastic cause for pancytopenia was much higher than that of non megaloblastic cause for pancytopenia.

Figure 13: RDW in patients with pancytopenia



This figure represent MPV in megaloblastic & non megaloblastic grouph. Mean platelet volume was used as a criteria to distinguish different cause for pancytopenia in other studies. In our study MPV was almost same between in megaloblastic [9.37±100] and non megaloblastic causes [9.34±0.99]

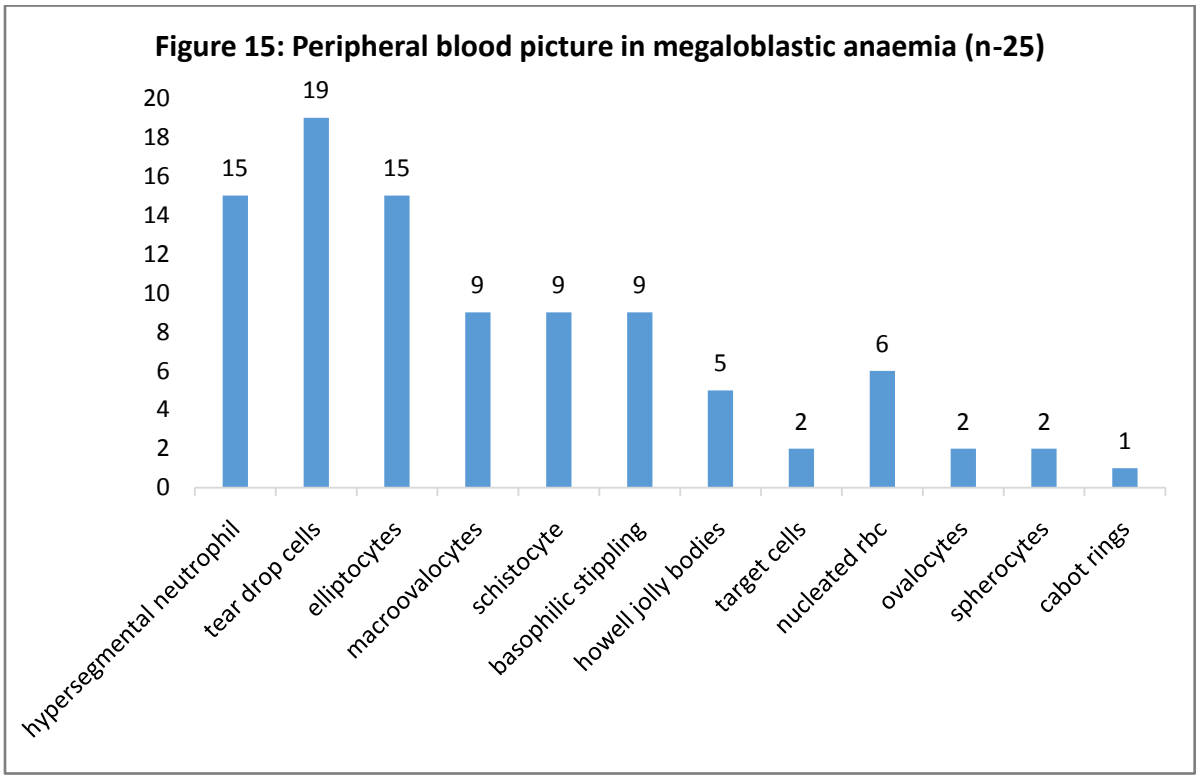


Table–11: Shows peripheral blood picture in pancytopenia patients. Anisopokilocytosis & hypersemental neutrophils was the predominant finding in megaloblastic anaemia. Immature WBC noted in acute myeloid leukemia, myelodysplastic syndrome, plasma cell dyscrasias.

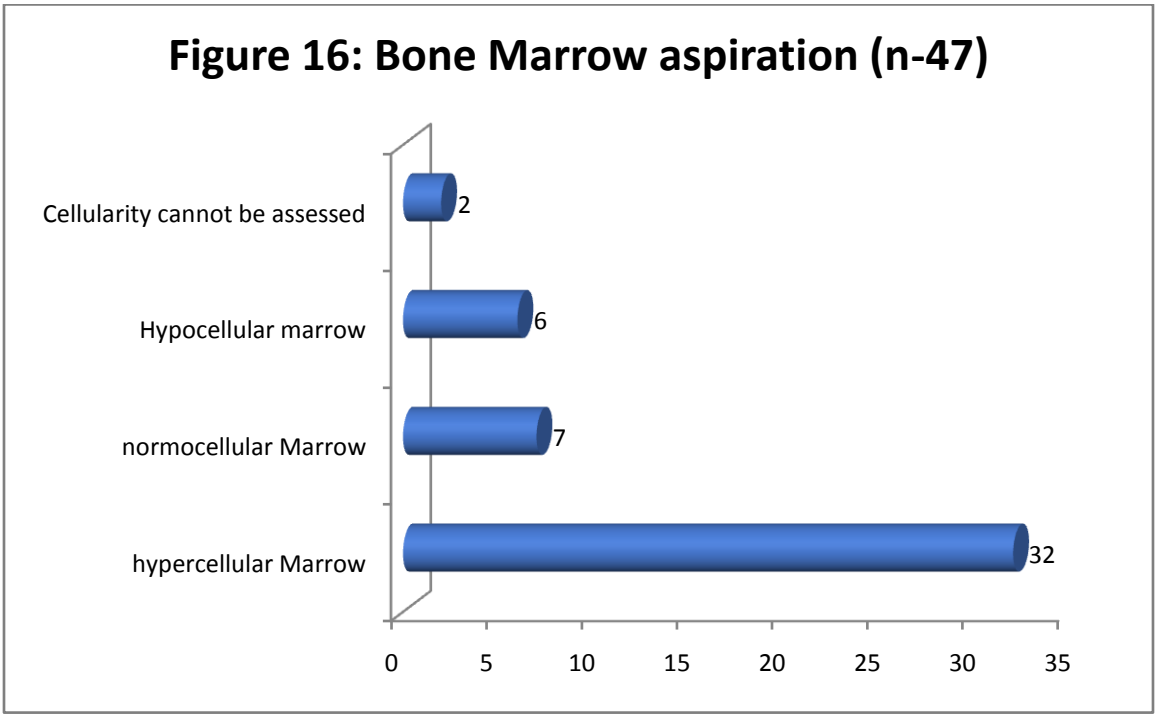
Causes	**No. of Patients**	**A**	**B**	**C**	**D**	**E**	**F**	**G**
Megaloblastic anaemia	**25**	24	3	15	3	5	0	0
Hypersplenism	**5**	5	0	0	0	0	0	0
aplastic anaemia	**4**	3	0	1	1	0	0	0
dengue fever with pre – existing iron deficiency anaemia	**4**	2	0	0	2	1	0	0
systemic lupus erythematosus	**2**	1	0	0	1	1	0	0
plasma cell dyscrasias	**2**	2	1	0	0	1	0	0
myelodysplastic syndrome	**2**	2	1	1	1	0	0	0
Hemophagocytic lymphohistiocytosis	**1**	1	0	0	0	0	0	0
acute myeloid leukemia	**1**	0	1	0	0	0	0	0
non hodgkins lymphoma	**3**	2	0	0	1	0	0	0
Total	**50**	**43**	**6**	**17**	**10**	**8**	**0**	**0**

A – ANISOPOIKILOCYTOSIS
B – IMMATURE WBC
C- HYPERSEGMENTED NEUTROPHILS
D – ACTIVATED LYMPHOCYTES
E – LYMPHOCYTOSIS
F – IMMATURE RBC
G – INCREASED RETICS

The various peripheral smear findings in patient with megaloblastic anaemia are as follows. The most common finding in our study is tear drop cells followed by hypersegmented neutrophil & elliptocytes.

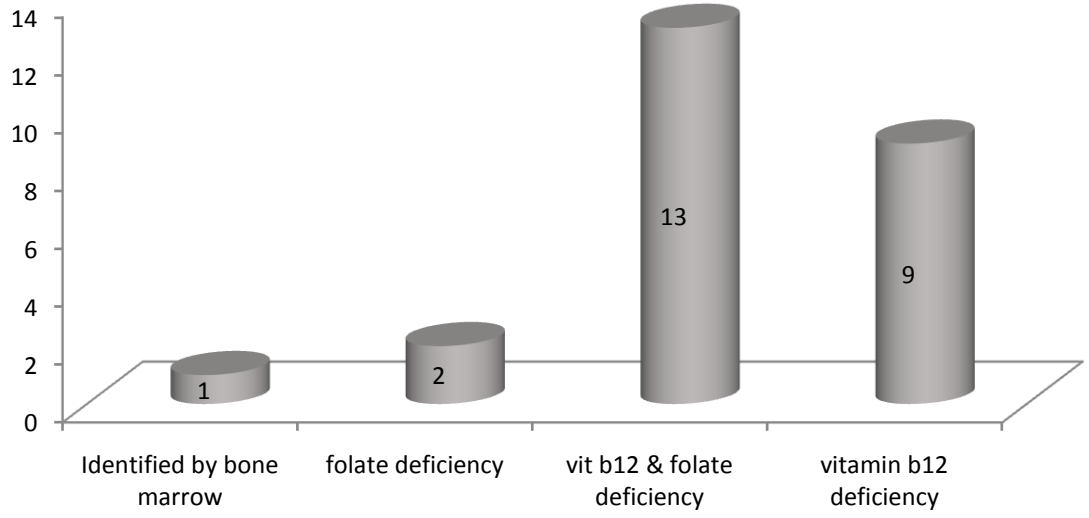


This figure represent bone marrow aspiration finding in pancytopenia patients. The most common finding in our study is hypercellular marrow [68.08%] followed by normocellular marrow [14.89%]. Out of 50 patients, 3 patient bone marrow aspiration and biopsy was not done.



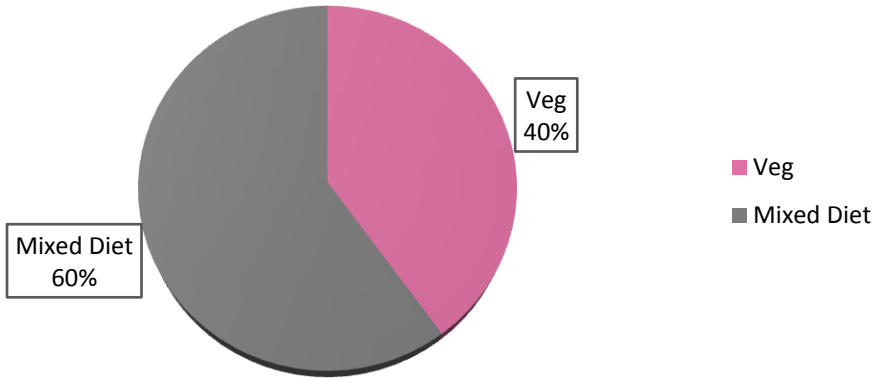
The cause for megaloblastic anaemia in our study group were as follows. Combined vitamin B12 & folate deficiency [52.0%] was the most common cause. Followed by isolated vitamin B12 deficiency [36.0%]. Isolated folate deficiency - 8%

Figure 17: nutrient deficiencies in patients with megaloblastic anaemia (n-57)



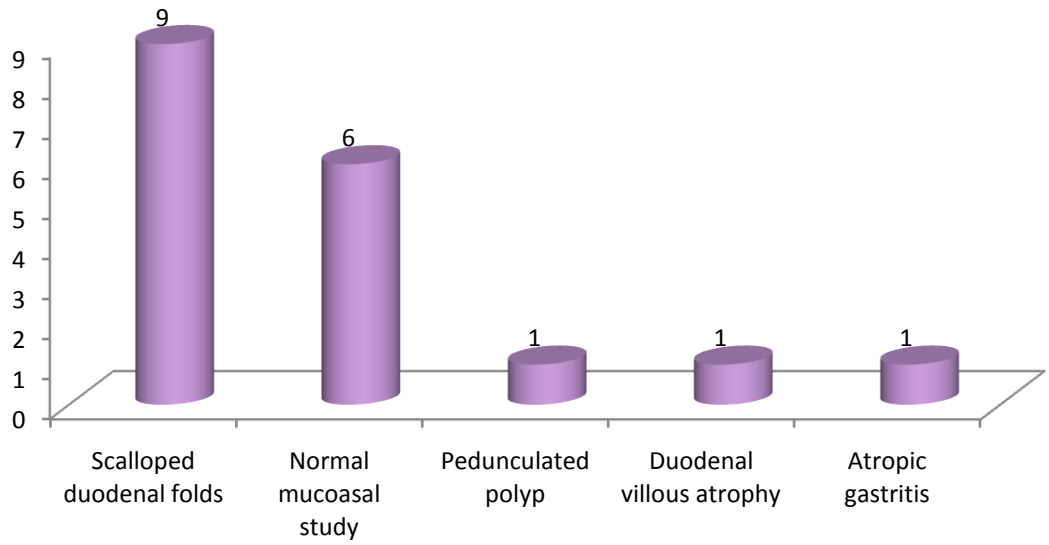
Of the 25 patient with megaloblastic anaemia 40% (n-10) were vegetarian diet, whereas 60% (n-15) consumed mixed diet.

Figure 18: % of vegetarians in the megaloblastic group

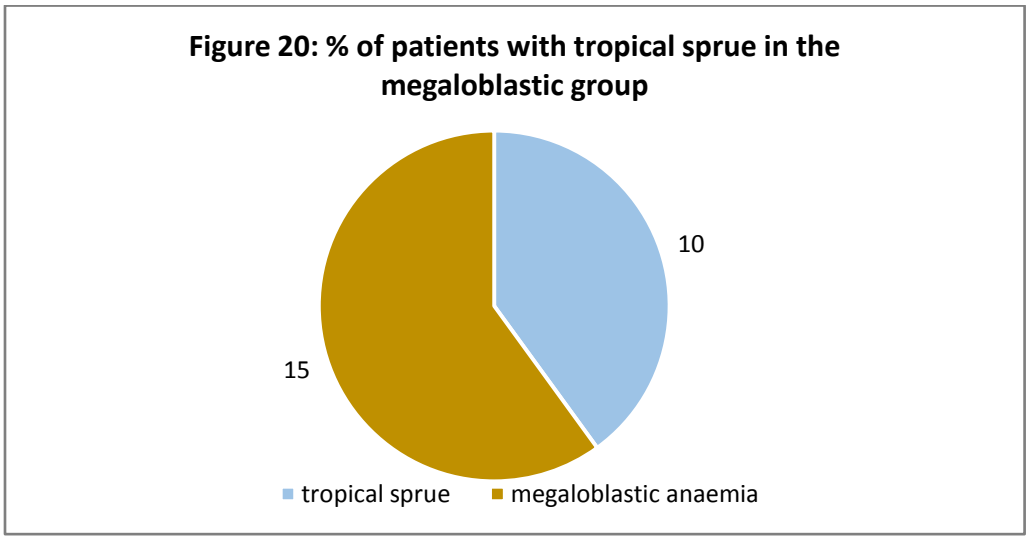


Endoscopic finding in patient in patient with megaloblastic anaemia are represented in the figure below.

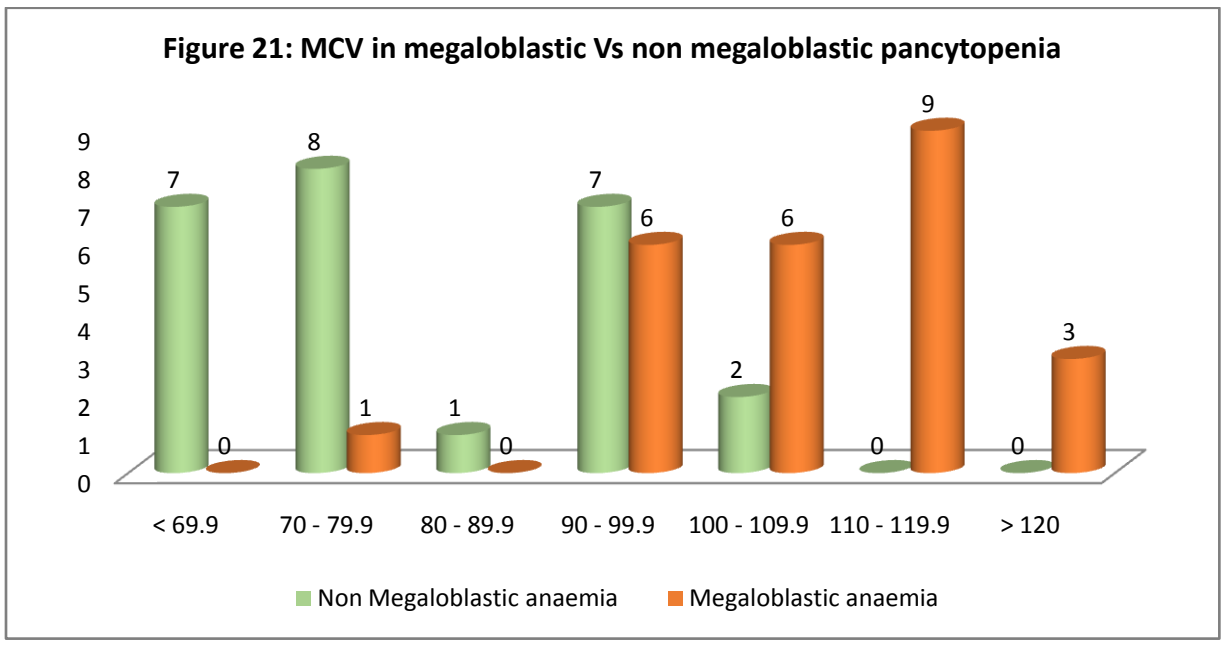
Figure 19: Endoscopic finding in patients with megaloblastic anaemia



Out of all the patients with megaloblastic anaemia as a cause for pancytopenia 17 patients consented & underwent endoscopy. Of these patients 10 [58.82%] had tropical sprue whereas only 41.17% had no evidence of tropical sprue in the biopsy.



MCV in megaloblastic & non megalobalastic anaemia. In our study, MCV value high in megaloblastic anaemia than non megaloblastic anaemia.



DISCUSSION

Most of the studies that have been done on pancytopenia in adults have included paediatric population as well. It is very important to do study specifically in adults because the physician treating children and adults are different and more importantly the aetiological of pancytopenia in paediatric is very different from the adult population. Various studies that have beendone in the paediatric population have shown that most common cause of pancytopenia is likely to be malignancy. In a study done by gupta et al at Banaras in children the most common cause for pancytopenia in children was aplastic anaemia 43% followed by acute leukemia 25%. Megaloblastic anaemia was the only the third common cause for pancytopenia in those children accounying only to about 6.7% of children. In a study done by zeb jan et al in Peshawar, Pakistan in children the total number of children included were 205 [age group 6 month to 14yrs]. In that study the most common cause for pancytopenia was aplastic anaemia which constituted 28.3% followed by haematological malignancy 23.9% & megaloblastic anaemia 19.5%. in another study done by khan et al in Pakistan where about 279 pancytopenic children were analysed the most common cause for pancytopenia was acute leukemia 32.2% followed by aplastic anaemia 30.8% & megaloblastic anaemia 13.2%. Though there have been few studies done in the adult population with regards to pancytopenia the major drawback of most of these studies has been that they have been done including quite a large number of paediatric patients which actually misguides the treating physician and does not give a clear view of the prevalence of the various etiological factors in adult population.

Figure 22: comparing the common etiologies in children with pancytopenia

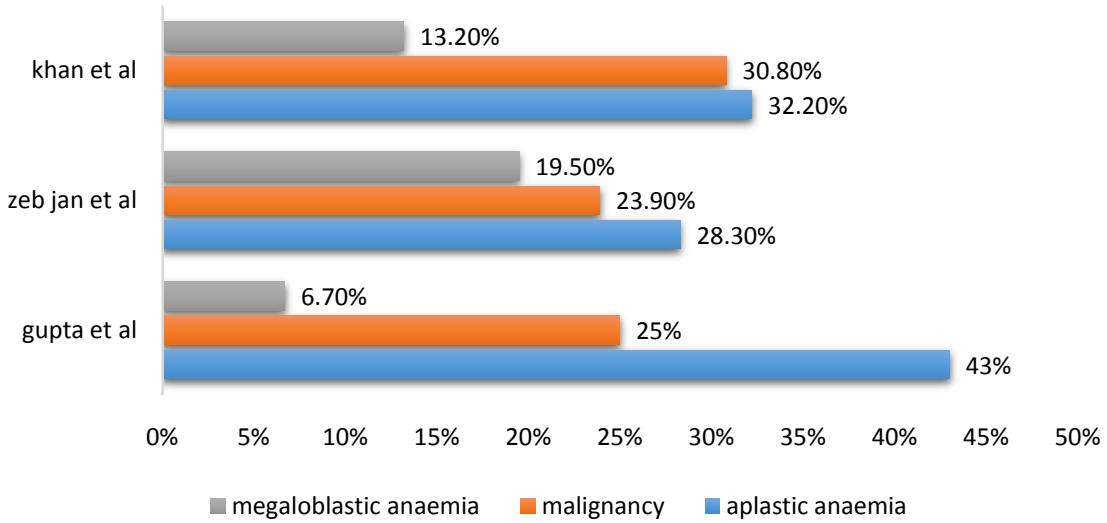
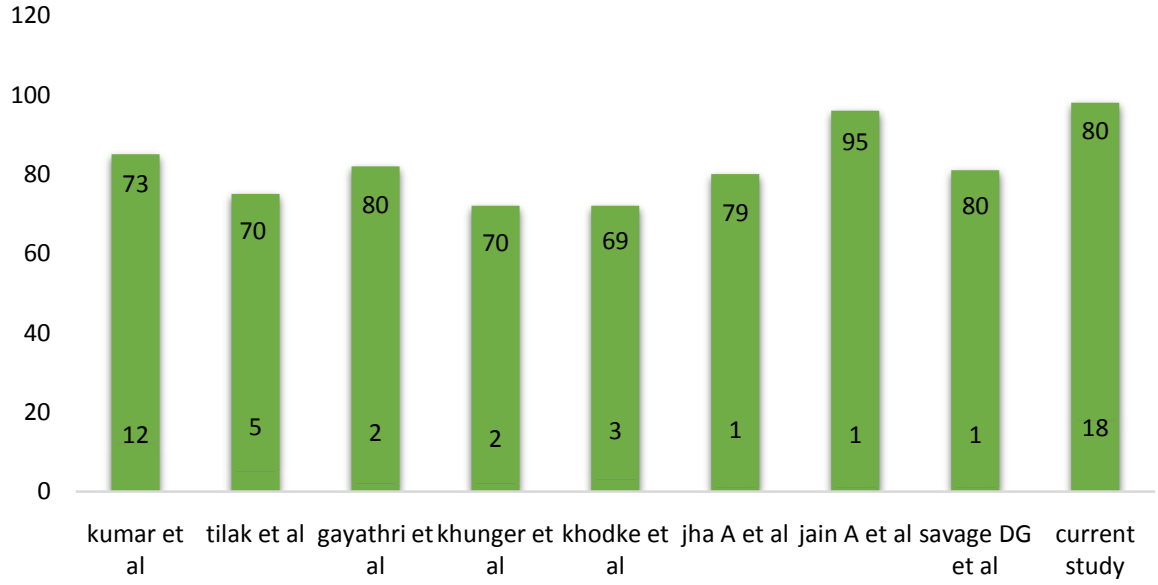


Figure 23: Comparison of age group in others & current study



The male to female ratio in most patients show a male preponderance in almost all studies. In our study showed a male: female ratio 1:1

TABLE–12: COMPARING MALE: FEMALE RATIO IN OTHER STUDIES

STUDY AUTHOR	MALE : FEMALE RATIO
Savage DG et al [113]	1.3:1
Tilak et al [110]	1.14:1
B N Gayathri et al [111]	1.2:1
Jha A et al [1122]	1.5:1
Kumar et al [110]	2.1:1
Khunger et al [108]	1.2:1
Kodke et al	1.3:1
Current study	1:1

Below **Table– 13:** Showing the author of the study, year of study, no of cases and study location.

Author	Location	Year of study	No of cases
Elizabeth et al	USA	2012	250
Imbert et al	France	1989	213
Savage et al	Zimbabwe	1999	134
Jha A et al	Nepal	2008	148
Kumar et al	Chandigargh, India	2001	166
Khunger et al	New Delhi, India	2002	200
B N Gayathri et al	Davangere, India	2011	104
Tilak et al	Chandigargh, India	1999	77
Current study	Coimbatore, India	2017	50

Figure 24: Comparison of haemoglobin values between our study and study done by gayathiri et al in megaloblastic group

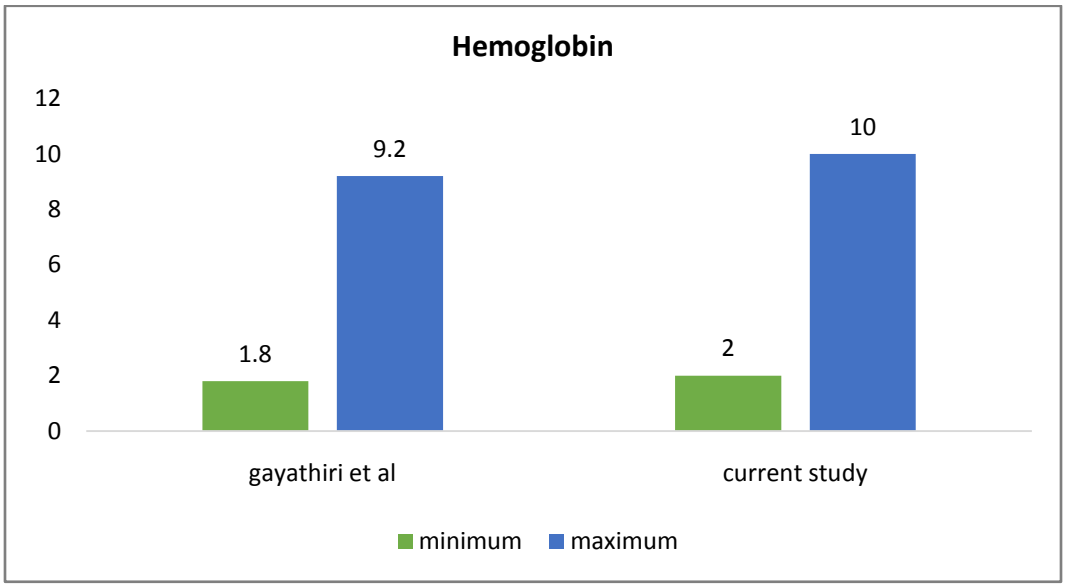


Figure 25: Comparison of total WBC values between our study and study done by gayathiri et al in megaloblastic group

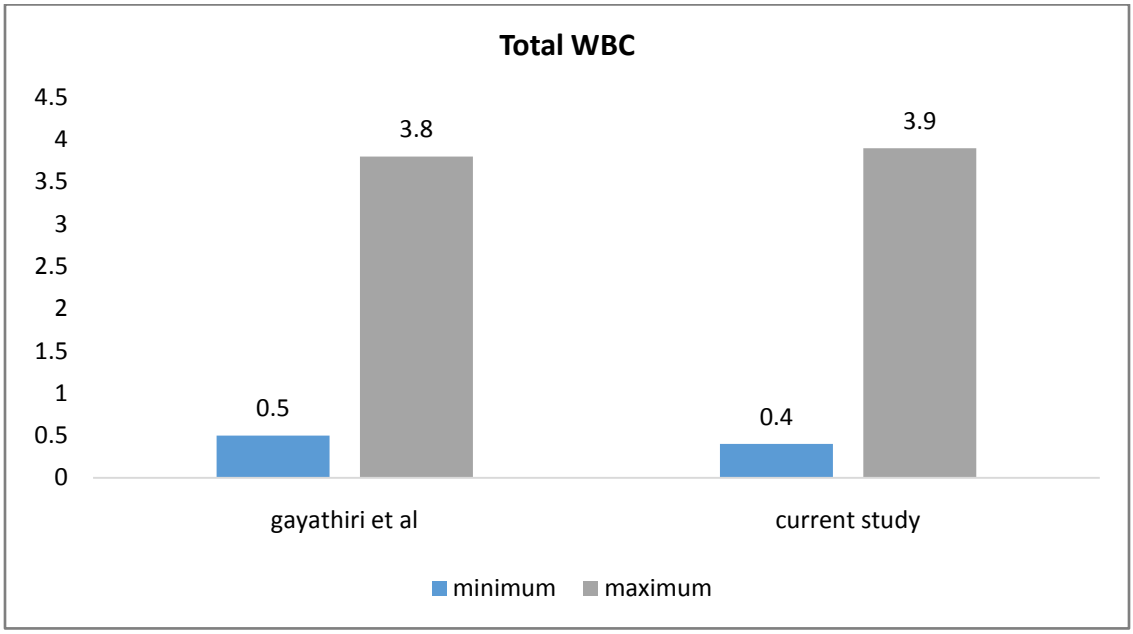
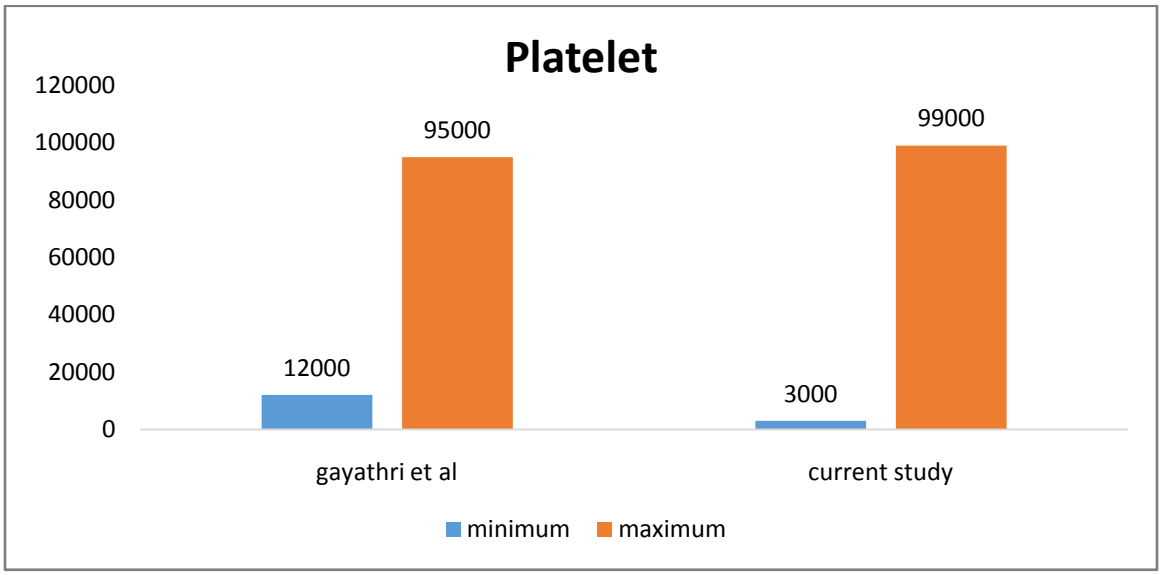
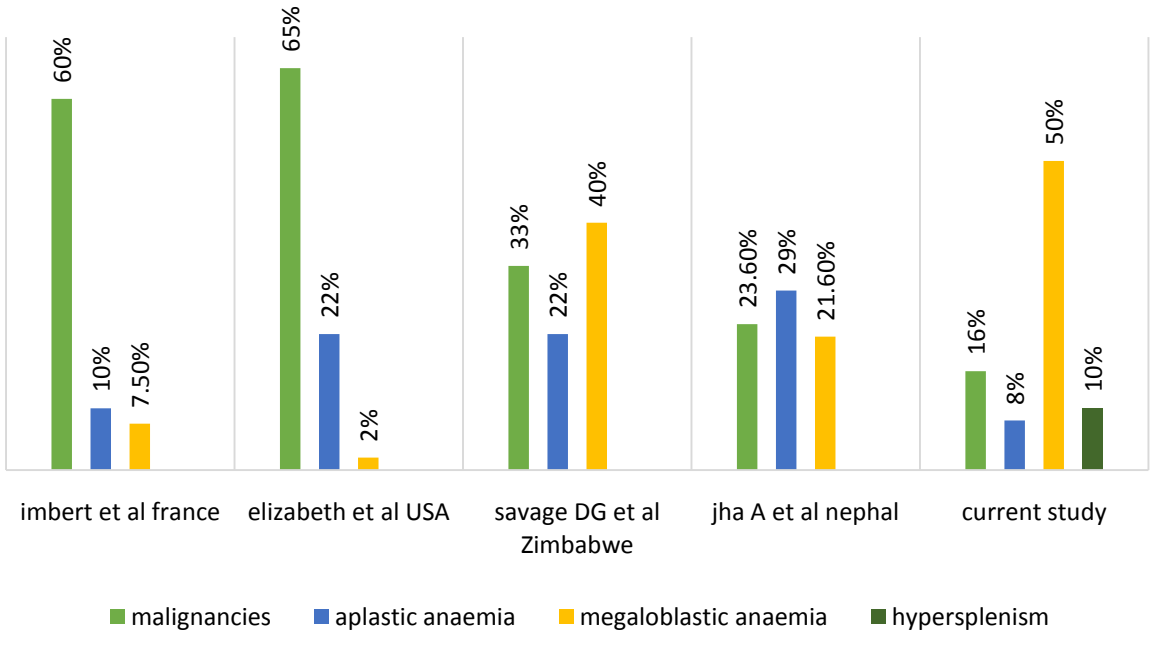


Figure 26: Comparison of platelet values between our study and study done by gayathiri et al in megaloblastic group



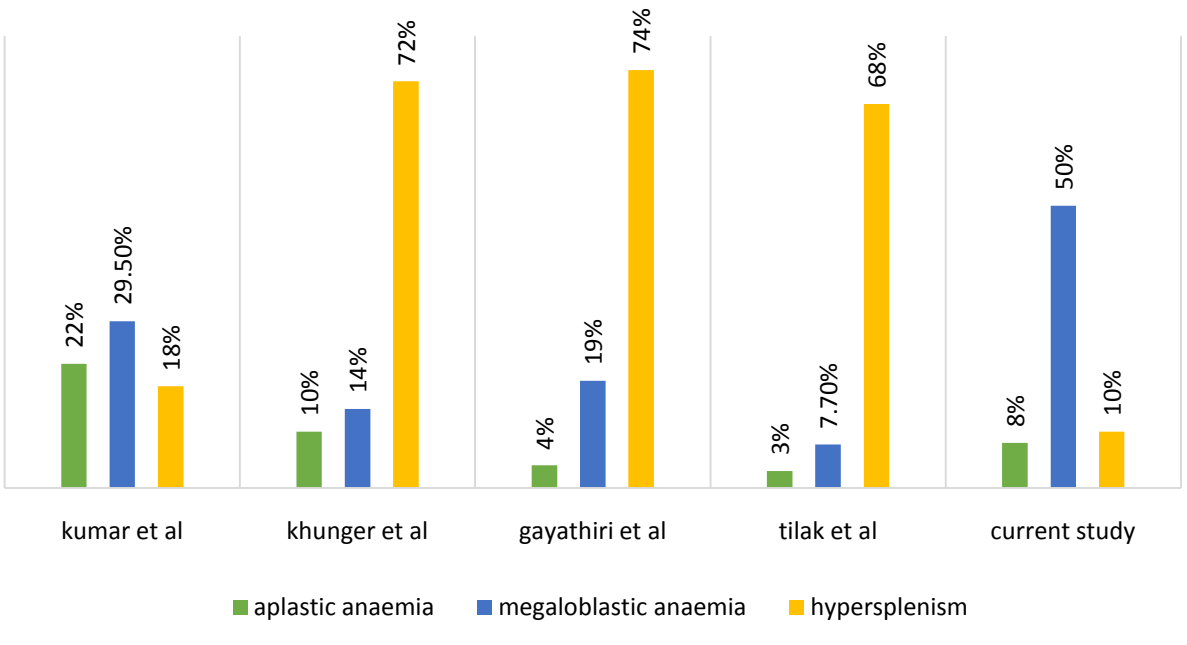
The most common causes of pancytopenia in various studies outside India are represented in the following figure. Imert et al & Elizabeth et al study clearly shows most common cause for pancytopenia is malignancies. Savage dg et al study done in Zimbabwe which shows most common cause is megaloblastic anaemia. Study done in nephal – jha a et al shows most common cause is aplastic anaemia followed by megaloblastic anaemia. In our study the most common cause for pancytopenia was megaloblastic anaemia followed by malignancies.

FIGURE 27: COMPARISON OF MOST COMMON CAUSES FOR PANCYTOPENIA WITH STUDIES DONE OUTSIDE INDIA



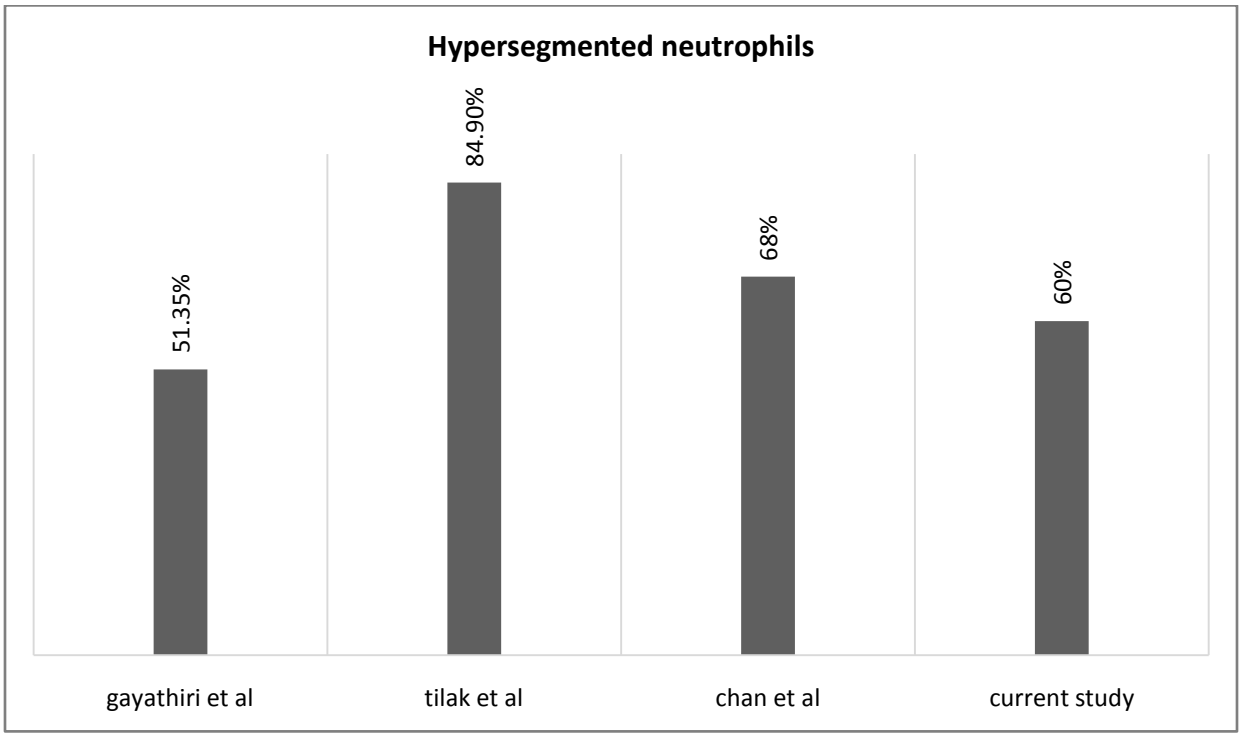
The figure shows current study compare with other Indian studies. Khunger et al, Gayathiri et al, Tilak et al shows most common cause for pancytopenia was hypersplenism, followed by megaloblastic anaemia. Kumar et al study shows common cause was megaloblastic anaemia. Current study shows most common cause is megaloblastic anaemia followed by hypersplenism.

FIGURE 28: COMPARISON OF MOST COMMON CAUSES FOR PANCYTOPENIA WITH STUDIES DONE IN india



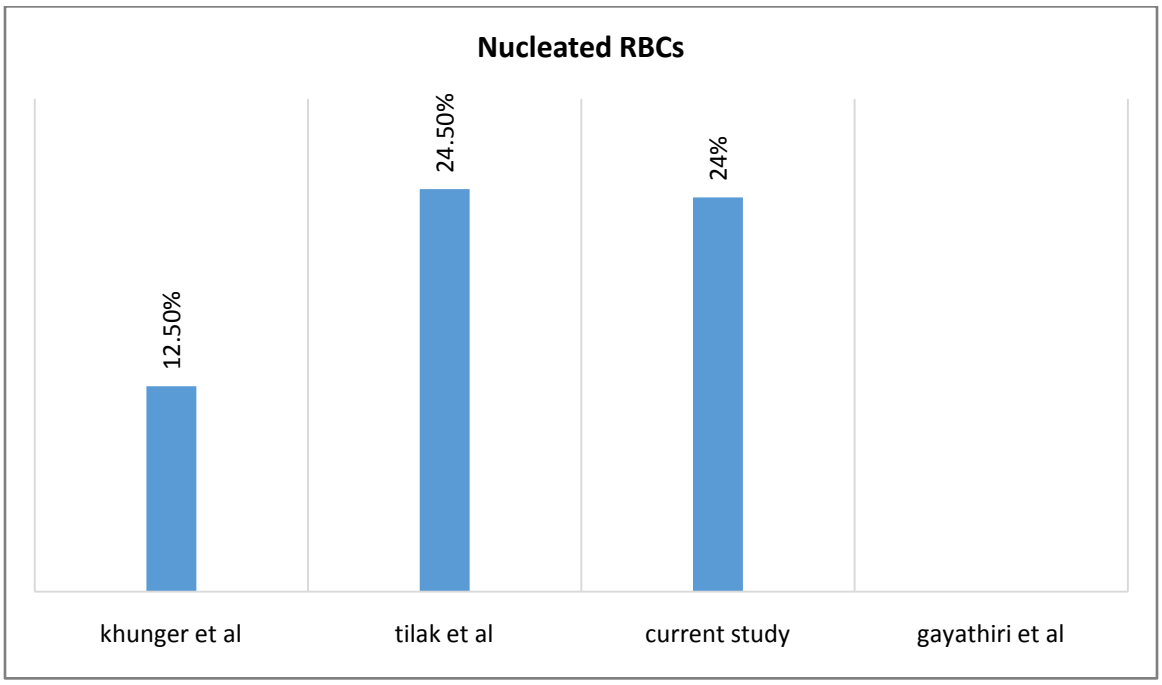
Hypersegmented neutrophils are characteristic feature of megaloblastic anaemia and the incidence has varied in different studies. In our study the presence of hypersegmental neutrophil was 60% when compared to 51.35%; 84.9% and 68% in gayathiri et al; tilak et al and chan et al respectively.

Figure 29: shows hypersegmented neutrophils prevalence in peripheral smear of megaloblastic anaemia patients in various studies.



Nucleated RBCs though not presented in classical literature has been present in 24% of the megaloblastic population in our study whereas the study by gayathiri et al reported no such finding; khunger et al has reported nucleated RBCs in 12.5% of the megaloblastic study population [n-144]; tilak et al have reported the presence of nucleated RBCs to be 24.5% in the megaloblastic subgroup in their study [n-53].

Figure 30: percentage of the megaloblastic group presenting with nucleated RBCs



RECOMMENDATIONS

- All patients presenting with pancytopenia should be evaluated for megaloblastic anaemia and other correctable factors
- Vitamin B12 & folate assay are useful tests in the evaluation of megaloblastic anaemia
- Upper GI endoscopy & deep duodenal biopsy should be done in all patients diagnosed to have megaloblastic anaemia to evaluate for tropical sprue
- Bone marrow aspiration & biopsy need not be done in most patients with a clinical picture of megaloblastic anaemia

CONCLUSION

From our study it can be proposed that inspite of numerous etiology available for pancytopenia and its various manifestations the most common etiology is the megaloblastic anaemia.

And the most common reason for megaloblastic anaemia is vitamin b12 deficiency. So it can be suggested that screening of b12 deficiency should be the intial screening test for evaluation of megaloblastic anaemia irrespective of the diet of the patient because it is not only the most common cause of megaloblastic anemia but is also present in patients who consume mixed diet. Other investigations like UGI scopy can be followed through if needed based on clinical scenario. Other conditions like malignancy, hypersplenism and aplastic anaemia which are the next most common cause in our study should also be kept in mind while ordering further investigations

The findings of the above study also indicates that prompt identification of patients with megaloblastic anemia and treating the underlying cause in intial stage itself can reduce the incidence of pancytopenia and its various complication.

LIMITATIONS

1. This study was conducted in particular region & most of the study population were natives of the same location, hence the race and regional variability cannot be comment upon
2. Few of the patients in this study denied bone marrow biopsy and UGI scopy hence, those finding not included in this study
3. Few of these patients were not followed through due poor patient compliance hence, response to therapy were not looked into in detailed.

REFERENCES

1. Gayathri BN, Rao KS. Pancytopenia: a clinico hematological study. Journal of laboratory physicians. 2011 Jan;3(1):15.
2. Jha A, Sayami G, Adhikari RC, Panta AD, Jha R. Bone marrow examination in cases of pancytopenia.
3. Gupta V, Tripathi S, Tilak V, Bhatia BD. A study of clinico-haematological profiles of pancytopenia in children. Tropical doctor. 2008 Oct;38(4):241-3.
4. Keisu M, Öst Å. Diagnoses in patients with severe pancytopenia suspected of having aplastic anemia. European journal of haematology. 1990 Jul 1;45(1):11
5. Khunger JM, Arulselvi S, Sharma U, Ranga S, Talib VH. Pancytopenia--a clinico haematological study of 200 cases. Indian journal of pathology & microbiology. 2002 Jul;45(3):375-9.
6. McPherson RA, Pincus MR. Henry's Clinical Diagnosis and Management by Laboratory Methods E-Book. Elsevier Health Sciences; 2017 Apr 5.
7. Den Ottolander GJ. The bone marrow aspirate of healthy subjects. British journal of haematology. 1996 Dec;95(3):574-5.
8. Chen B, Mao B, Huang S, Zhou Y, Tsuji K, Ma F. Human embryonic stem cell-derived primitive and definitive hematopoiesis. InPluripotent Stem Cell Biology-Advances in Mechanisms, Methods and Models 2014. InTech.

9. LEE SH, Erber WN, Porwit A, Tomonaga M, Peterson LC. ICSH guidelines for the standardization of bone marrow specimens and reports. International journal of laboratory hematology. 2008 Oct 1;30(5):349-64.
10. Riley RS, Ben-Ezra JM, Pavot DR, Forysthe R, Massey D, Wright L, Smith E. An illustrated guide to performing the bone marrow aspiration and biopsy.
11. Devaliaf V, Tudor G. Bone marrow examination in obese patients. British journal of haematology. 2004 May 1;125(4):538-9.
12. Marshall PN. Methylene blue-azure B-eosin as a substitute for May-Grunwald-Giemsa and Jenner-Giemsa stains. Microscopica acta. 1977 Mar;79(2):153-6.
13. Wittekind D. On the nature of Romanowsky dyes and the Romanowsky- Giemsa effect. International Journal of Laboratory Hematology. 1979 Dec 1;1(4):247-62.
14. Malempati S, Joshi S, Lai S, Braner DA, Tegtmeyer K. Bone marrow aspiration and biopsy. N Engl J Med. 2009 Oct 8;361(15):28.
15. Brook MG, Ayles H, Harrison C, Rowntree C, Miller RF. Diagnostic utility of bone marrow sampling in HIV positive patients. Sexually Transmitted Infections. 1997 Apr 1;73(2):117-21.
16. Kaferle J, Strzoda CE. Evaluation of macrocytosis. American family physician. 2009 Feb 1;79(3).
17. Hoffbrand V, Provan D. ABC of clinical haematology. Macrocytic anaemias. BMJ: British Medical Journal. 1997 Feb 8;314(7078):430.

18. Colon-Otero G, Hook CC, Menke D. A practical approach to the differential diagnosis and evaluation of the adult patient with macrocytic anemia. Medical Clinics of North America. 1992 May 1;76(3):581-97.
19. d'Onofrio G, Chirillo R, Zini G, Caenaro G, Tommasi M, Micciulli G. Simultaneous measurement of reticulocyte and red blood cell indices in healthy subjects and patients with microcytic and macrocytic anemia. Blood. 1995 Feb 1;85(3):818-23.
20. Hesdorffer CS, Longo DL. Drug-induced megaloblastic anemia. New England Journal of Medicine. 2015 Oct 22;373(17):1649-58.
21. Karvellas CJ, Sawyer M, Hamilton M, Mackey JR. Effect of capecitabine on mean corpuscular volume in patients with metastatic breast cancer. American journal of clinical oncology. 2004 Aug 1;27(4):364-8.
22. Snower DP, Weil SC. Changing etiology of macrocytosis: zidovudine as a frequent causative factor. American journal of clinical pathology. 1993 Jan 1;99(1):57-60.
23. Burns ER, Reed LJ, Wenz B. Volumetric erythrocyte macrocytosis induced by hydroxyurea. American journal of clinical pathology. 1986 Mar 1;85(3):337-41
24. Engström KG, Löfvenberg E. Treatment of myeloproliferative disorders with hydroxyurea: effects on red blood cell geometry and deformability. Blood. 1998 May 15;91(10):3986-91.

25. Gillessen S, Graf L, Korte W, Cerny T. Macrocytosis and cobalamin deficiency in patients treated with sunitinib. New England Journal of Medicine. 2007 May 31;356(22):2330-1.
26. Gillessen S, Graf L, Korte W, Cerny T, Aliberti S, Grignani G, Allione P, Khasawneh MF, Unnithan J, Choueiri T. Macrocytosis due to treatment with sunitinib. N Engl J Med. 2007 Sep 27;2007(357):1351-2.
27. Rini BI, Choueiri TK, Elson P, Khasawneh MK, Cotta C, Unnithan J, Wood L, Mekhail T, Garcia J, Dreicer R, Bukowski RM. Sunitinib- induced macrocytosis in patients with metastatic renal cell carcinoma. Cancer. 2008 Sep 15;113(6):1309-14.
28. Schallier D, Trullemans F, Fontaine C, Decoster L, De Greve J. Tyrosine kinase inhibitor-induced macrocytosis. Anticancer research. 2009 Dec 1;29(12):5225-8.
29. Rajaraman S, Davis WS, Mahakali-Zama A, Evans HK, Russell LB, Bedell MA. An allelic series of mutations in the Kit ligand gene of mice. II. Effects of ethylnitrosourea-induced Kitl point mutations on survival and peripheral blood cells of Kitl Steel mice. Genetics. 2002 Sep 1;162(1):341-53.
30. Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis. Clinical medicine & research. 2006 Sep 1;4(3):236-41.
31. Sanvisens A, Zuluaga P, Pineda M, Fuster D, Bolao F, Junca J, Tor J, Muga R. Folate deficiency in patients seeking treatment of alcohol use disorder. Drug & Alcohol Dependence. 2017 Nov 1.

32. Latvala J, Parkkila S, Melkko J, Niemelä O. Acetaldehyde adducts in blood and bone marrow of patients with ethanol-induced erythrocyte abnormalities. Molecular Medicine. 2001 Jun;7(6):401.
33. Wickramasinghe SN, Malik F. Acetaldehyde causes a prolongation of the doubling time and an increase in the modal volume of cells in culture. Alcoholism: Clinical and Experimental Research. 1986 May 1;10(3):350-4.
34. Horton L, Coburn RJ, England JM, Himsworth RL. The haematology of hypothyroidism. QJM: An International Journal of Medicine. 1976 Jan 1;45(1):101-23.
35. Westerman DA, Evans D, Metz J. Neutrophil hypersegmentation in iron deficiency anaemia: a case-control study. British journal of haematology. 1999 Dec;107(3):512-5.
36. Beard ME, Weintraub LR. Hypersegmented neutrophilic granulocytes in iron deficiency anaemia. British journal of haematology. 1969 Jan 1;16(1):161-4.
37. Jensson O. Observations on the leucocyte blood picture in acute uraemia. British journal of haematology. 1958 Oct 1;4(4):422-7.
38. Edwards MJ, Penny RH. Effects of hyperthermia on the myelograms of adult and fetal guinea- pigs. British journal of haematology. 1985 Jan 1;59(1):93-101.
39. Morioka N, Otsuka F, Nogita T, Igisu K, Urabe A, Ishibashi Y. Neutrophilic dermatosis with myelodysplastic syndrome: nuclear segmentation anomalies of neutrophils in the skin lesion and in peripheral blood. Journal of the American Academy of Dermatology. 1990 Aug 1;23(2):247-9.

40. Wakatsuki S, Hirokawa M, Horiguchi H, Kanahara T, Manabe T, Sano T. Hypersegmentation of inflammatory cells in Langerhans cell granulomatosis. Diagnostic cytopathology. 2000 Oct 1;23(4):238-41.
41. Zak M, Rezný Z, Uhlirova A, Bednarova Z, Lintner L, Benes J. Dependence of the postirradiation lymphopenia and hypersegmentation of neutrophil nuclei on the therapeutic irradiation exposure in patients with breast carcinoma--some ways of its use for biological detection of irradiation. Strahlentherapie. 1978 Dec;154(12):852-7.
42. Eichacker P, Lawrence C. Steroid- induced hypersegmentation in neutrophiles. American journal of hematology. 1985 Jan 1;18(1):41-5.
43. Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. The American journal of medicine. 1994 Mar 1;96(3):239-46.
44. Carmel R, Green R, Jacobsen DW, Rasmussen K, Florea M, Azen C. Serum cobalamin, homocysteine, and methylmalonic acid concentrations in a multiethnic elderly population: ethnic and sex differences in cobalamin and metabolite abnormalities. The American journal of clinical nutrition. 1999 Nov 1;70(5):904-10.
45. Carmel R, Green R, Rosenblatt DS, Watkins D. Update on cobalamin, folate, and homocysteine. ASH Education Program Book. 2003 Jan 1;2003(1):62-81.

46. Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. The American journal of medicine. 1994 Mar 1;96(3):239-46.
47. Allen RH, Stabler SP, Savage DG, Lindenbaum J. Diagnosis of cobalamin deficiency I: usefulness of serum methylmalonic acid and total homocysteine concentrations. American journal of hematology. 1990 Jun 1;34(2):90-8.
48. Miller JW, Garrod MG, Rockwood AL, Kushnir MM, Allen LH, Haan MN, Green R. Measurement of total vitamin B12 and holotranscobalamin, singly and in combination, in screening for metabolic vitamin B12 deficiency. Clinical chemistry. 2006 Feb 1;52(2):278-85.
49. Hvas AM, Nexo E. Holotranscobalamin as a predictor of vitamin B12 status. Clinical chemistry and laboratory medicine. 2003 Nov 17;41(11):1489-92.
50. Herrmann W, Obeid R, Schorr H, Geisel J. Functional vitamin B12 deficiency and determination of holotranscobalamin in populations at risk. Clinical chemistry and laboratory medicine. 2003 Nov 17;41(11):1478-88.
51. Nilsson K, Isaksson A, Gustafson L, Hultberg B. Clinical utility of serum holotranscobalamin as a marker of cobalamin status in elderly patients with neuropsychiatric symptoms. Clinical chemistry and laboratory medicine. 2004 Jun 7;42(6):637-43.

52. Herrmann W, Obeid R, Schorr H, Geisel J. The usefulness of holotranscobalamin in predicting vitamin B12 status in different clinical settings. Current drug metabolism. 2005 Feb 1;6(1):47-53.
53. Chen X, Remacha AF, Sardà MP, Carmel R. Influence of cobalamin deficiency compared with that of cobalamin absorption on serum holo-transcobalamin II. The American journal of clinical nutrition. 2005 Jan 1;81(1):110-4.
54. Carmel R, Rasmussen K, Jacobsen DW, Green R. Comparison of the deoxyuridine suppression test with serum levels of methylmalonic acid and homocysteine in mild cobalamin deficiency. British journal of haematology. 1996 May 1;93(2):311-8.
55. Wickramasinghe SN, Saunders JE. Results of three years' experience with the deoxyuridine suppression test. Acta haematologica. 1977;58(4):193-206.
56. Carmel R, Karnaze DS. The deoxyuridine suppression test identifies subtle cobalamin deficiency in patients without typical megaloblastic anemia. Jama. 1985 Mar 1;253(9):1284-7.
57. Wickramasinghe SN, Longland JE. Assessment of deoxyuridine suppression test in diagnosis of vitamin B12 or folate deficiency. Br Med J. 1974 Jul 20;3(5924):148-50.
58. Jones, P., Grace, C.S. and Rozenberg, M.C., 1979. Interpretation of serum and red cell folate results. A comparison of microbiological and radioisotopic methods. *Pathology*, *11*(1), pp.45-52.

59. Phekoo K, Williams Y, Schey SA, Andrews VE, Dudley JM, Hoffbrand AV. Folate assays: serum or red cell?. Journal of the Royal College of Physicians of London. 1997;31(3):291-5.
60. Jaffe JP, Schilling RF. Erythrocyte folate levels: a clinical study. American journal of hematology. 1991 Feb 1;36(2):116-21.
61. Clifford AJ, Noceti EM, Block-Joy A, Block T, Block G. Erythrocyte folate and its response to folic acid supplementation is assay dependent in women. The Journal of nutrition. 2005 Jan 1;135(1):137-43.
62. Owen WE, Roberts WL. Comparison of five automated serum and whole blood folate assays. American journal of clinical pathology. 2003 Jul 1;120(1):121-6.
63. Bain BJ, Wickramasinghe SN, Broom GN, Litwinczuk RA, Sims J. Assessment of the value of a competitive protein binding radioassay of folic acid in the detection of folic acid deficiency. Journal of clini
64. Allen RH, Stabler SP, Savage DG, Lindenbaum J. Diagnosis of cobalamin deficiency I: usefulness of serum methylmalonic acid and total homocysteine concentrations. American journal of hematology. 1990 Jun 1;34(2):90-8.
65. Carmel R. How I treat cobalamin (vitamin B 12) deficiency. Blood. 2008 Sep 15;112(6):2214-21.
66. Ferraro S, Mozzi R, Panteghini M. Tracing a roadmap for vitamin B12 testing using the health technology assessment approach. Clinical Chemistry and Laboratory Medicine (CCLM). 2014 Jun 1;52(6):767-77.

67. Charkin S. BNF recommends hydroxocobalamin rather than cyanocobalamin for vitamin B12 deficiency. BMJ. 2014 Sep 3;349:g5389.
68. Glynn J. Tropical sprue—its aetiology and pathogenesis. Journal of the Royal Society of Medicine. 1986 Oct;79(10):599-606.
69. Lv Y, Lau WY, Li Y, Deng J, Han X, Gong X, Liu N, Wu H. Hypersplenism: History and current status. Experimental and therapeutic medicine. 2016 Oct 1;12(4):2377-82.
70. Kalambokis G, Tsianos EV. Endotoxaemia in the pathogenesis of cytopenias in liver cirrhosis. Could oral antibiotics raise blood counts?. Medical hypotheses. 2011 Jan 31;76(1):105-9.
71. Zuchini R, Huang CH, Tsai HW, Huang SC, Lin CP, Chen CY, Lee GB, Lin XZ. Electromagnetic thermoablation to treat thrombocytopenia in cirrhotic and hypersplenic rats. Journal of gastroenterology and hepatology. 2010 Sep 1;25(9):1578-86.
72. Chernykh ER, Starostina NM, Paltsev AI, Leplina OY, Shevela EY, Shipunov MV, Selihova YB, Kulagin AD, Lisukov IA, Nikonov SD, Ostanin AA. Autologous bone marrow cells in the treatment of cirrhosis of the liver. Bulletin of experimental biology and medicine. 2007 Oct 1;144(4):640-5.
73. Zhang W, Zhang S, Li ZF, Huang C, Ren S, Zhou R, Jiang A, Yang AN. Knockdown of PIK3R1 by shRNA inhibits the activity of the splenic macrophages associated with hypersplenism due to portal hypertension. Pathology-Research and Practice. 2010 Nov 15;206(11):760-7.

74. Kenawi MM, El- Ghamrawi KA, Mohammad AA, Kenawi A, El- Sadek AZ. Splenic irradiation for the treatment of hypersplenism from congestive splenomegaly. British journal of surgery. 1997 Jun 1;84(6):860-1.
75. Sankararaman S, Velayuthan S, Vea R, Herbst J. Severe gastric variceal bleeding successfully treated by emergency splenic artery embolization. Pediatrics International. 2013 Jun 1;55(3).
76. Krishnan SK, Hill A, Hillmen P, Arnold LM, Brooksbank GL, Wood A, Scarsbrook A, Davies MH, Kelly RJ. Improving cytopenia with splenic artery embolization in a patient with paroxysmal nocturnal hemoglobinuria on eculizumab. International journal of hematology. 2013 Dec 1;98(6):716-8.
77. N'kontchou G, Seror O, Bourcier V, Mohand D, Ajavon Y, Castera L, Grando-Lemaire V, Ganne-Carrie N, Sellier N, Trinchet JC, Beaugrand M. Partial splenic embolization in patients with cirrhosis: efficacy, tolerance and long-term outcome in 32 patients. European journal of gastroenterology & hepatology. 2005 Feb 1;17(2):179-84.
78. Ishigami M, Ishizu Y, Onishi Y, Kamei H, Kiuchi T, Itoh A, Hirooka Y, Katano Y, Goto H. Long-term dynamics of hematological data and spleen volume in cirrhotic patients after liver transplantation-various dynamics depending on etiology. Springerplus. 2013 Dec 1;2(1):374.
79. Weledji EP. Benefits and risks of splenectomy. International Journal of Surgery. 2014 Feb 28;12(2):113-9.

80. Marsh JC, Ball SE, Cavenagh J, Darbyshire P, Dokal I, Gordon- Smith EC, Keidan J, Laurie A, Martin A, Mercieca J, Killick SB. Guidelines for the diagnosis and management of aplastic anaemia. British journal of haematology. 2009 Oct 1;147(1):43-70.
81. Goss JA, Schiller GJ, Martin P, Seu P, Stribling R, McDiarmid SV, Shackleton CR, Markowitz JS, Nuesse BJ, Goldstein LI, Busuttil RW. Aplastic anemia complicating orthotopic liver transplantation. Hepatology. 1997 Oct 1;26(4):865-9.
82. Walport MJ, Hubbard WN, Hughes GR. Reversal of aplastic anaemia secondary to systemic lupus erythematosus by high-dose intravenous cyclophosphamide. British medical journal (Clinical research ed.). 1982 Sep 18;285(6344):769.
83. Nissen C. Pathophysiology of aplastic anaemia. Acta haematologica. 1991;86(2):57-60.
84. Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. Blood. 2006 Oct 15;108(8):2509-19.
85. Shichishima T, Okamoto M, Ikeda K, Kaneshige T, Sugiyama H, Terasawa T, Osumi K, Maruyama Y. HLA class II haplotype and quantitation of WT1 RNA in Japanese patients with paroxysmal nocturnal hemoglobinuria. Blood. 2002 Jul 1;100(1):22-8.
86. Marsh JC, Ball SE, Cavenagh J, Darbyshire P, Dokal I, Gordon- Smith EC, Keidan J, Laurie A, Martin A, Mercieca J, Killick SB. Guidelines for the diagnosis

and management of aplastic anaemia. British journal of haematology. 2009 Oct 1;147(1):43-70.

87. Doney K, Leisenring W, Storb R, Appelbaum FR. Primary treatment of acquired aplastic anemia: outcomes with bone marrow transplantation and immunosuppressive therapy. Annals of Internal Medicine. 1997 Jan 15;126(2):107-15.

88. Storb R, Leisenring W, Anasetti C, Appelbaum FR, Buckner CD, Bensinger WI, Chauncey T, Clift RA, Deeg HJ, Doney KC, Flowers ME. Long-term follow-up of allogeneic marrow transplants in patients with aplastic anemia conditioned by cyclophosphamide combined with antithymocyte globulin. Blood. 1997 May 15;89(10):3890.

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

To
Dr M Mallan Prakash
Postgraduate
Department of General Medicine
Guide: Dr T Saravanan
PSG IMS & R
Coimbatore

Ref: Project No.16/097

Date: May 9, 2016

Dear Dr Mallan Prakash,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 25.02.2016 to conduct the research study entitled "*Clinico hematological study in pancytopenia patient presenting to tertiary care hospital*" during the IHEC meeting held on 07.03.2016.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol (Version 1 dated 25.02.2016)
3. Informed Consent Forms (Version 1 dated 25.02.2016)
4. Data collection tool
5. Permission letter from concerned Head of the Department
6. Current CVs of Principal investigator, Co-investigators
7. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 07.03.2016 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr R Nandakumar (Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr Sudha Ramalingam	MD	Epidemiologist, Ethicist Alt. member-Secretary	Female	Yes	Yes
4	Dr D Vijaya	M Sc., Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
   d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
   e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
   f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

STUDY PROFORMA

1. IP NUMBER:
2. SEX:
3. AGE:
4. OCCUPATION:
5. SOCIO ECONOMIC STATUS:
6. ADDRESS:

7. COMORBID CONDITIONS:

8. CHEIF COMPLAINTS:

9. MEDICAL HISTORY:

10. CLINICAL EXAMINATION:

11. ALL BASE LINE INVESTIGATION:

    COMPLETE BLOOD COUNT

PERIPHERAL BLOOD PICTURE

RETICULOCYTE COUNT

ANEMIA PROFILE

SERUM VITAMIN B12 AND FOLIC ACID LEVEL

MALARIAL PARASITE

LACTATE DEHYDROGENASE AND URIC ACID

VIRAL MARKERS (HbsAg,HCV,HIV)

THYROID FUNCTION TEST

LIVER AND RENAL FUNCTION TEST

CHEST X-RAY

USG ABDOMEN

BONE MARROW ASPIRATION AND BIOPSY

<u>IF REQUIRED SPECIFIC INVESTIGATION DONE:</u>

ANA, ANA IF AND RHEUMATOID FACTOR

CMV,EBV

SERUM COAGULATION PROFILE,FIBRINOGEN AND D-DIMER

COOMBS TEST

TUBERCULIN TEST

UGI SCOPY

IMMUNOPHENOTYPHING

CYTOGENETICS

IMMUNOELECTROPHORESIS

DIEPOXYBUTANE

LYMPH NODE BIOPSY

12. FOLLOW UP BONE MARROW ASPIRATION AND BIOPSY REPORTS

13. COMPLETE BLOOD COUNT BEFORE DISCHARGE PATIENTS

14. STATISTICAL WORK UP

15. SUBMISSION

பூ. சா. கோ மருத்துவக் கல்லூரி மற்றும் ஆராய்ச்சி நிறுவனம், கோவை

மனித நெறிமுறைக் குழு

ஒப்புதல் படிவம்

தேதி:

மரு. ம. மல்லன் பிரகாஷ் ஆகிய நான் பூ. சா. கோ மருத்துவக் கல்லூரியின் / மருத்துவமனையின் பொது துறையின் கீழ், "கிளினிக்கோ ஹெமட்டாலாஜிக்கள் பான்சைட்டோபீனியா நோயாளிகளுக்கான ஆய்வு" என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்.

என் ஆய்வு வழிகாட்டி: மரு. டி. சரவணன்

ஆய்வு மேற்கொள்வதற்கான அடிப்படை:

தென்னிந்தியாவில் கிளினிக்கோ ஹெமட்டாலாஜிக்கள் பான்சைட்டோபீனியா நோயாளிகளுக்கான ஆய்வுகளும் அதற்கான கரணங்களும் போதிய அளவில் இல்லாத காரணத்தினால், அதனை கண்டறிய இந்த ஆய்வினை மேற்கொள்கிறேன்.

ஆய்வின் நோக்கம்:

பான்சைட்டோபீனியாவுக்கு காரணமான பல்வேறு காரணிகளை கண்டறிய உடல் பரிசோதனை, இரத்த மாதிரிகள், மற்றும் எலும்பு மஜ்ஜை ஆய்வுகள் மூலம் கண்டறிதல்.
பான்சைட்டோபீனியாவுக்கு காரணமான பல்வேறு காரணிகளின் நிகழ்வுகள் மதிப்பீடு செய்தல்.

ஆய்வில் பங்கு பெறும் நபர்களின் எண்ணிக்கை: 2016 - 2017

ஆய்வில் பங்கு பெறுவோர் மற்றும் வயது: 16 வயதுக்கு மேற்பட்டோர், சிவப்பு அனுக்கள் <10g/dl, வெள்ளை அனுக்கள் <4000, தட்டனுக்கள் <1,00,000 குறைவாக உள்ளவர்கள்.

ஆய்வு மேற்கொள்ளும் இடம்: பூ. சா. கோ மருத்துவ கல்லூரி மருத்துவமனை, கோயமுத்தூர்

இந்த ஆய்வில் எங்களுடன் ஒத்துழைக்குமாறு கேட்டுக்கொள்கிறோம். நாங்கள் சில தகவல்களை இந்த ஆய்விற்காக சேகரிக்க உள்ளோம்.

ஆய்வு செய்யப்படும் முறை:

முதன்மை நேர்காணல்: **10-15 நிமிடங்கள்**

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் **3 வருடங்கள்** பாதுகாக்கப்படும். இந்த தகவல்கள் வேறு ஆய்விற்குப் பயன்படுத்தப் படும்/பயன்படுத்தப் பட மாட்டாது.

மருத்துவ பரிசோதனைகள்:

இரத்த மாதிரி சேகரிப்பு: 2 மிலி, ஒருமுறை / இரண்டு முறை

இரத்த மாதிரி எடுப்பது வழக்கமான சிகிச்சைக்காகவோ அல்லது இந்த ஆய்விற்காகவோ: குறிப்பிட்ட ஆய்விற்காக

இதனால் ஏற்படக் கூடிய அசௌகரியங்கள் / பக்க விளைவுகள்: இதனால் எந்த அசௌகரியமோ, பக்க விளைவுகளோ ஏற்படாது.

இரத்த மாதிரிகள் ஆய்விற்குப் பின் பாதுகாத்து வைக்கப்படுமா? ஆம் / இல்லை, அழிக்கப்படும்: **இல்லை**

சேகரிக்கப்பட்ட இரத்தம் விற்கப்படுமா? ஆம் / இல்லை **இல்லை**

சேகரிக்கப்பட்ட இரத்தம் வேறு நிறுவனத்துடன் பகிர்ந்து கொள்ளப்படுமா? ஆம் / இல்லை: **இல்லை**

மருந்துகள் ஏதேனும் கொடுக்கப் பட்டிருந்தால் அவை பற்றிய விவரம் (கொடுக்கப்பட்ட காரணம், காலம், பக்க விளைவுகள், பயன்கள்) **இல்லை**

மருந்துகள் கொடுக்கப்படுவது வழக்கமான சிகிச்சை முறையா? ஆம் / இல்லை (ஆம் என்றால் இந்த குறிப்பிட்ட மருந்து கொடுக்கப்பட்டதன் கரணம்)

ஆய்வில் பங்குபெறுவதால் ஏற்படும் பலன்கள்:
ஆய்விற்குட்பட்ட நோயாளிகளிள் பான்சைட்டோபீனியாவுக்கு காரணமான பொதுவான காரணிகளை கண்டறிதல். நோயின் தன்மை கண்டறிதல் அல்லது பான்சைட்டோபீனியாவுக்கு காரணமான காரணிகளை கண்டு நீக்குதல், மேலும் பான்சைட்டோபீனியாவுக்கான சிகிச்சை மற்றும் மருத்துவ பரிசோதனைக்கு பயனுள்ளதாக இருக்கும்.

ஆய்வின் முடிவுகள் எந்த முறையில் பயன்படுத்தப்படும்?
ஆய்வின் முடிவுகள், அடுத்தகட்ட ஆராய்ச்சிகளுக்கும், மருத்துவ ஆய்வு பத்திரிக்கைகளில் வெளியிடுவதற்கும் பயன்படுத்துப்படும்.

இந்த ஆய்வின் கேள்விகளுக்கு பதிலளிப்பதோ, இரத்த மாதிரிகள் அல்லது திசு மாதிரிகள் எடுப்பதிலோ உங்களுக்கு ஏதேனும் அசௌகரியங்கள் இருந்தால், எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு. எப்பொழுது வேண்டுமானாலும் ஆய்விலிருந்து விலகும் உரிமை உங்களுக்கு உள்ளது. ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சை

முறையில் எந்த வித பாதிப்பும் இருக்காது என்று உங்களுக்கு உறுதியளிக்கிறோம். மருத்துவ மனையில் நோயாளிகளுக்கு அளிக்கப்படும் சேவைகளை நீங்கள் தொடர்ந்து பெறலாம். இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்ளுவதால் வேறு எந்த விதமான கூடுதலான பலனும் உங்களுக்குக் கிடைக்காது. நீங்கள் அளிக்கும் தகவல்கள் இரகசியமாக வைக்கப்படும். ஆய்வில் பங்கேற்பவர்கள் பற்றியோ அவர்கள் குடும்பத்தைப் பற்றியோ எந்தத் தகவலும் எக்காரணம் கொண்டும் வெளியிடப்படாது என்று உறுதியளிக்கிறோம். நீங்கள் அளிக்கும் தகவல்கள் / இரத்த மாதிரிகள் / திசு மாதிரிகள் அங்கீகரிக்கப்பட்ட ஆய்விற்கு மட்டுமே பயன்படுத்தப்படும். இந்த ஆய்வு நடைபெறும் காலத்தில் குறிப்பிடத்தகுந்த புதிய கண்டுபிடிப்புகள் அல்லது பக்க விளைவுகள் ஏதும் ஏற்பட்டால் உங்களுக்குத் தெரிவிக்கப்படும். இதனால் ஆய்வில் தொடர்ந்து பங்கு பெறுவது பற்றிய உங்கள் நிலைப்பாட்டை நீங்கள் தெரிவிக்க ஏதுவாகும்.

ஆய்வுக்குட்படுபவரின் ஒப்புதல்: இந்த ஆய்வைப் பற்றிய மேற்கூறிய தகவல்களை நான் படித்து அறிந்து கொண்டேன் / ஆய்வாளர் படிக்கக் கேட்டுத் தெரிந்து கொண்டேன். ஆய்வினைப் பற்றி நன்றாகப் புரிந்து கொண்டு இந்த ஆய்வில் பங்கு பெற ஒப்புக்கொள்கிறேன். இந்த ஆய்வில் பங்கேற்பதற்கான எனது ஒப்புதலை கீழே கையொப்பமிட்டு . கை ரேகை பதித்து நான் தெரிவித்துக் கொள்கிறேன்.

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தேதி :

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MASTER CHART

NAME	IP NO	AGE	SEX	DIAGNOSIS	SYMPTOMS	EXAMINATION	HB	WBC	PLT	PERIPHERAL SMEAR	ANAEMIA PROFILE	BA	BX	OTHER TEST	FOLLOW UP
										ps- pancytopenia & myeloblast. Mild anisocytosis. Blast 15%. One blast demonstrate auer rods+.**immature wbc +++**	s.iron-80, tibc-236, ferritin-936	acute myeloid leukemia with dysplasia of myeloid lineage	**hypocellular marrow** with features compatiable with bone marrow aspiration diagnosis of acute leukemia	mcv - 99, wit b12 - 394, folate-3.52, tsh-2.970, hiv,hbsag,hcv - negative. Scrub typhus-neg, cmv-neg, weilfelix test - neg. ana profile - neg. EBV-neg. usg abd-hepatomegaly	
rehana begum	I17002036	53	f	acute myeloid leukemia	**fever, fatigueability**	hepatomegaly+	7.3	2.2	13						
				megaloblastic anaemia-vit b12 & folate deficiency [mixed diet]	**dyspnea, fatigueability**, vomiting	pallor, icterus+, spleenomegaly+	4.6	3.2	82	moderate anisopoikilocytosis & microcytic normochromic to macrocytic hypochromic. **Anisopoikilocytosis + &** hypersemented neutrophils +,**polychromasia+,**elliptocytes+,tear drop cells+.	nd	hypercellular & florid erythroid hyperplasiam with predominant megaloblastic maturation. Occassional gaint metamelocytes are seen	**hypercellular marrow** - erythroid hyperplasia	MCV- 115,rdw- 24.4,mpv -10.1, vit b12 -<50.0, folate-1.32, LDH- 3333, hepatoglobin- <10, esr-97, tsh- 2.80, usg abd- splenomegaly, duodenal biopsy - tropical sprue[scalloped duodenal folds]	20 days later - rpt Hb-12, tc- 7.8, PLT- 261
mayilsamy	I16036799	41	m												
				megaloblastic anaemia-vit b12 & folate deficiency [veg]	**fatigue ability, dyspnea**	pallor+, pedal edema +	4.9	3.9	9	macrocytic normochromic anemia - **anisopoikilocytosis +, lymphocytosis +**,elliptocytes+,tear drop cells+,**target cells+,polychromasia+,**basophilic stippling+,howell jolly bodies+.	s.iron-121, tibc- 133, ferritin- >2000	hypercellular & shows marked erythroid hyperplasia characterized by normoblastic as well as megaloblastic maturation. Myeloid series shows sequential maturation with occasional gaint band forms.	**hypercellualr marrow** - erythroid hyperplasia with megaloblastic	MCV-108,rdw-25.7,mpv-10.6, idh-477 corrected reticulocyte count - 0.4%, dengue serology-neg,EBV,CMV -neg, viral serology - neg. ana profile - ss-A +, SCL-70 +. Usg abd - minimal ascities, minimal rt pleural effussion, duodenal biopsy- tropical spure[lax lower esophageal sphincter & **scalloping of duodenal folds**],vitamin b12-125,folate-4.22	2 months later rpt Hb-12.1, wbc-8.9, plt-398
Thiyagu	I16037240	29	m												
				non hodgkins lymphoma - small lymphocytic lymphoma [SLL] & vitamin b12 deficiency	**loss of appetite,fatigueability, dyspnea+, palpitation & weight loss+**	pedal edema+, hepatomegaly+, spleenomegaly+	3.3	1.5	12	macrocytic normochromic anaemia - **anisoookilocytosis+**	not done	in adequate	bone trabeculae enclosing hypercellular marrow spaces. Marrow spaces shows infiltration by sheets of small round cells with scanty cytoplasm & round hyperchromatic	mcv-95. ldh- 117. vitamin B12- 113. folate- 10.4. viral serology neeative	10 days later- hb-7.6, wbc-1.6, plt-10
rabiya	I16022796	60	f												
ramya	I16023185	38	f	dengue fever with hepatitis	**fever,mylagia,headache**	mild pallor+	10	3	80	normocytic normochromic anemia - **lymphocytosis ++ & activated lymphocytes +**	not done	not done	not done	mcv-76,sgot-248, sgpt-127, mcv-76,dengu igm postive, usg abdomen-normal	rpt Hb-11,tc-5.5,plt-245,sgpt-40,sgot-33
				megaloblastic anaemia-vitamin B12 deficiency [mixed diet]	**loss of appetite, weight loss** -10kg	pallor+	6.8	3.2	36	dimorphic anaemia - predominantly macrocytic normochromic. **Anisopoikilocytosis +,**elliptocytes+,tear drop cells+,basophilic stippling+,**polychromasia+,**schistocytes+	not done	hypercellular for age & show erythroid series show megaloblastic maturation with mild dyserythropoiesis[nuclear budding/briding,howell jolly bodies]ring neutrophils+,multinucleated megakaryocytes + - f/s/o megaloblastic anaemia	**hypercellular marrow** - erythroid series show -hyperplasia with megaloblastic maturation. Myeloid precursors- sequential maturation with occasional gaint forms, few megakaryocytes seen.	mcv-108,rdw-37.2,mpv-8.3,idh-2808,vitamin B12 -<30,folate -5.94, **[not done]**	no follow up
dharmaraj	I16022964	76	m												
pavithra	I16026297	22	f	acute febrile illness, extra hepatic portal vein obstruction, **hypersplenism**	**fever,headache**	pallor,massive spleenomegaly+	7.9	0.4	38	microcytic hypochromic anaemia with leukopenia . **Anisopoikilocytosis+**	iron-31,tibc-284,ferritin-33	trilineage hematopoiesis with lymphocytosis	**normocellular** - trilineage hematopoiesis with focal mild increase in lymphocytes	mcv-73,tsh-1.90,ft4-1.01,folate-8.51,vitamin b12-286, ldh-166,usg colour doppler abdomen- chronic portal venous occlusion;gross spleenomegaly;portal hypertension. Usg abdomen- gross splenomegaly,narrow calibre portal vein with thin flow. Ugi scopy-grade a esophagitis, lax les,bile reflux gastritis	1 month later- hb-10.2,tc-3.3,plt-64. 2 month later-hb-12,tc-4.7,plt-69. 5 month later - hb-12.1,tc-4.6,plt -54
balamurgan	I16026213	23	m	**myelodysplastic syndrome**	**lee swelling,fatigueability**	pallor+,pedal edema+,facial puffiness+	8.2	3.2	9	normocytic normochromic to microcytic hypochromic anaemia with thrmbocytopenia. **Anisoopilocytosis+,activated lymphocytes+**	not done	hypercellular, erythropoesis-normoblastic to megaloblastic maturation[dyserythropoiesis], myelopoiesis-suppressed with sequential maturation,gaint bands & myelocytes are seen [dysgranulopoiesis + ,megakaryopoiesism-decreased. Abnormal cells [blast-8%], increased N:C ratio,irregular nuclei & 1-2 prominent nucleoli.	**normocellular marrow** with megakaryocytic hypoplasia & dysplasia & aggregates of suspicious cells.	mcv-86,vitamin b12-1536,folate-7.86,ldh-203,uric acid-2.1,hiv-neg,usg abdomen-normal. Alp-192	
sarasa	I16026940	55	f	massive splenomegaly with **hypersplenism**, folate deficiency, portal hypertension, ? Non cirrhotic portal fibrosis, esophageal varices,hypothyrdism	**abdominal distension,malena,blood vomitus,h/o weight loss+ &diarrhoea**	pallor+,b/l pedal edema+,massive splenomegaly+	5.6	1.3	49	microcytic hypochromic to normocytic hypochromic anemia - **marked anisopoikilocytosis+**	iron-22,tibc-452,ferritin-10	f/s/o-combimed nutritional deficiency anemia with predominatly iron deficiency component with reactive megakaryocytic hyperplasia	**normocellular to mildly hypercellular** - suboptimal biopsy showing erythroid hyperplasia	mcv-73,viral serology- negative, tsh-97,ft4-0.17.vitamin B12-596,folate-3.78,lft-normal,usg colour doppler abdomen-f/s/o portal hypertension;ugi scopy-esophageal varices grade 2-3,mild portal gastropathy. Usg abdomen- chronic liver parenchymal disease with portal hypertension,gross splenomegaly,minimal free fluiss in pelvis.	10 days later-hb-9.7,tc-3.3,plt-65. 1 month later hb-10.9,tc-1.9,plt-57. ceruloplasmin-28.9. ANA prifile & liver profile - negative.
kalaiselvan	I16032921	50	m	megaloblastic anaemia-vitamin B12 deficiency [mixed diet]	**yellowish discolouration of eyes,loss of appetite,abdominal discomfort,easy fatigueability,dyspnea, weight loss+**	pallor+,icterus+	5.5	3.8	82	macrocytic normochromic anaemia - **severe anisopoikilocytosis+ &** hypersegmental neutrophils+,elliptocytes+,tear drop cells+,	iron-177,tibc-293,ferritin-291	megaloblastic anemia with ineffective hematopoiesis - bone marrow smear are hypercellular due to marked erythroid hyperplasia, erythropoiesis show megaloblastic maturation with dysplastic features.	**hypercellular marrow** - erythroid hyperplasia	mcv-100.3, rdw-40.5,mpv9.8,ana profile & ana if -neg, hiv-neg,duodenal biopsy-tropical sprue[lax lower esophageal sphincter,duodenogastric reflux **normal**],LDH-8945,vitamin B12-56,folate-5.44,anti TPO-8.16, reticucyte count -uncorrected - 1.0, usg abdomen - subtle coarse echotexture of liver.	15 days later hb-11.0,tc-5.7,plt-545
sivasamy	I16032474	26	m	megaloblastic anaemia-vitamin B12 & folate deficiency, hypothyrodism, addisons disease[veg]	**fever, loose stools, fatiguability**	pallor+, hyperpigementation of palms and tounge.	3.5	2	98	**anisopoikilocytosis**, **hypersemental neutrphils+,polychromasia+, nucleated rbc+,**elliptocytes+,tear drop cells+,**schitocytes+,gaint platelets+** - predominantly macrocytic normochromic anemia	iron-272,tibc-311,ferritin-128	f/s/o - megloblastic anemia [2008]	**hypercellular marrow** - f/c/w megaloblastic anemia	mcv116.8,rdw-25.3,mpv-11.6,vitamin B12-96,folate-3.91,tsh-12.90,ft4-1.35,lft-bilirubin[t]-2.9,[d]-0.9,[id]-2.0,duodenal biopsy-tropical sprue[lax lower esophageal sphincter,duodenogastric reflux, **normal**]	5 months later , hb-17.5,tc-8.6,plt-143
damodharan	I16038970	65	m	megaloblastic anaemia [veg] - vitamin b12 & folate deficiency	**fatigueability,giddiness+**	pallor+	6.9	3	79	macrocytic normochromic anaemia - **anisopoikilocytosis+,** hypersegmental neutrophils+,elliptocytes+,tear drop cells+,basophilic stppling+,macro ovalocytes+.	not done	inadequate	**hypercellular marrow**	mcv-98, rdw-32.3,mpv-9.2,vitamin B12-90,folate-1.79, tsh-3.010,LDH-1101,retic count- 0.1%,bilirubin[t]-1.6,[d]-0.5,[id]-1.1,hiv-neg,usg abdomen-liver shows subtle echotexture,duodenal biopsy- tropical sprue[lax lower esophageal sphincter,fundic gland polyp,scalloping fold]	no follow up
shanthamani	I16039449	50	f	megaloblastic anaemia-vitamin B12 & folate deficiency [veg]	**fatiguability,loss of appetite**	pallor+,pedal edema+,jvp raised	3.1	3.4	52	dimorphic anaemia- **anisopoikilocytosis+** hypersemental neutrophils+,elliptocytes+,tear drop cells+,basophilic stippling+,macroovalocytes+.	iron-148,tibc-209,ferritin-207	megaloblastic erythroid hyperplasia + bare nuclei	**hypercelluar marrow** - megaloblastic erythroid hyperplasia	mcv-96,rdw-32.3,mpv-9.2,ldh-6628,corrected retic count-0.03, ana profile & ana if -neg, vit B12-777,folate-3.38,tsh-2.370,ft4-1.35,ldh-6628,lft - bilirubin[t]-1.8,[d]-0.5,[id]-1.3, duodenal biopsy-non specific duodenitis[lax lower esophagel sphincter,fundic gland polyp,scalloping fold]	2 months later, hb-12.1,tc-8.4,plt-238
bangaru	I16039102	70	f	light chain myeloma	**hip joint pain,loss of appetite, weight loss**	pallor+,pedal edema+,b/ axillary lymph node +,hepatomegaly+,splenomegaly +	4.6	2	10	macrocytic normocytic normochromic. Atypical cells/blast-13% - **anisopikicocytosis +, immature wbc++**	not done	presence of immature cells[blast] mixed with few mature plasma cells against the background of exaggerated rouleux formation suggg- possibility of plasma cell dyscrasia	**cellularity cannot be assesed** - f/s/o-plasma cell dyscrasia consistent with myeloma. >5% of the immature cells are CD138 postive.scattered cells are also seen to be MPO postive	mcv-99.1,esr-120,corrected retic count-1.0,urine bence zones protein - neg,protein[t]-5.8,alb-3.1,glo-2.7,vitamin B12-830,folate-5.08,LDH-357.uric acid-6.9,protein electrophoresis-indictes a decrease in albumin with an elevated in gamma globulin,no abnormal bands.viral serology -neg,usg abdomen-hepatomegaly,splenomegaly,dilated portalvein. flow cytometry for acute leukemia pannel & immunofixation study showed IgG +ve, light chain kappa & lambda elevated.	no follow up
jaya suriyan	I17003345	17	m	megaloblatic anaemia-vitamin B12 deficiency [veg]	**loss of appetite,fatigueability,malena,**giddiness,vomiting	pallor+	7.3	2.1	82	macrocytic normochromic anemia- **anisopoikilocytosis+,**hypersemental neutrophils+,**microcytes+,**elliptocytes+,tear drop cells+,schistocytes+.	iron-50,tibc-287,ferritin-320	hypercellular,marked erythroid hyperplasia which displays megaloblastic maturation, dyserythropoesis in the form of nuclear budding,nuclear bridging,multi nuclearity and howel jolly bodies is seen - megaloblastic anemia with ineffective hematopoiesis.	**hypercellular marrow** - megaloblastic erythropoiesis	mcv-110,rdw-34.7,mpv-8.7,esr-63,vitamin B12-117,folate-3.07,anti TPO-13.51,tsh-0.839,ft4-1.09,idh-3351,bilirubin[t]-2.1,[d]-0.6,[id]-1.5,hiv-neg,ana profile & ana if -neg,usg abdomen- mild splenomegaly,duodenal biopsy - tropical sprue[lax lower esophagel sphincter,scalloping fold],anti ttg-negative.	10 days later,hb-9.9,tc-6.9,plt-498. 6 months later, hb-15.9,mcv-86,tc-8.3,plt-202
sangeetha	I17005328	21	f	dengue fever	**fever,mylagia, headache+**	pallor+	9.5	2.7	10	normocytic hypochromic anaemia with bicytopenia - **anisopoikilocytosis & activated lymphocytes +**	not done	not done	not done	mcv-76,smear for mp-neg,dengue IgM -postive,sgpt-38,sgot-91	no follow up
ganeshan	I17004160	51	m	megaloblastic anaemia - vitamin b12 & folate deficiency [mixed diet]	**dyspnea,yellowish discolourisation of skin+,fatiguability**	pallor+	4.2	1.9	18	macrocytic & microcytic hypochromic anemia - **anisopoikilocytosis,**hypersegmental neutrophils+ **& activated lymphocytes+,**macroovalocytes+,tear drop cells+,schistocytes+,elliptocytes+,howell jolly bodies,nucleated rbcs+,**gaint platelets+.**	iron-280,tibc-314,ferritin-455	f/c/w- megaloblastic anemia	**hypercellular marrow** - normoblastic to megaloblastic erythroid hyperplasia	mcv-118,rdw-25.1,mpv-8.0,esr-90,corrected retic count-0.48,vitamin B12-87,folate-1.40,ldh-783,bilirubin[t]-2.2,[d]-0.7,[id]-1.5,viral serology -neg,Duodenal-biopsy - peptic duodenit,D-1-gastric hetrotopia,gastric biopsy. h.pylori ass with chronic gastritit[erythematous & antral gastritis **normal**],usg abd-mild coarse liver echotexture,mild prostatomegaly	10 days later hb-8.4,mcv-100,tc-9.0,plt-524
nandhakumar	I17000110	27	m	megaloblastic anemia[diagnosed based on bone marrow] [mixed diet]	**fever,giddiness**	pallor+,icterus+,hyperpigmentation + over palms & soles,spleenomegaly	6.4	3.9	98	Microcytic hypochromic to macrocytic normochromic anaemia - **anisopoikilocytosis+,** hypersegmental neutrophils+ **& lymphocytosis**, macrovalocytes,tear drop cells **polychromasia,**spherocytes,nucleated rbcs **,gaint platelets+**	not done	erythroid hyperplasia with megaloblastic maturation & significant dyspoiesis especially in the megakaryocyte	**hypercellular marrow** with megaloblastic erythroid hyperplasia	mcv-115,rdw-26.3,mpv-11.5,esr-106,vitamin b12-404,folate-6.89,cortisol-11.61,viral serology-neg,dengue & scrub - neg.usg abdomen-fatty liver,splenomegaly+,duodenal biopsy-peptic duodenitis **[scalloping folds]**	no follow up
sinduja	I16040193	23	f	aplastic anemia	**bleeding per vagina, fatigueability,purpuritic spot over the hands & legs+**	purpuritic spots+ lower limb	7.3	3.6	29	macrocytic normochromic anemia- **anisopoikilocytosis+,hypersemental neutrophils+**	not done	f/s/o - megloblastic anemia	**hypocellular** with patchy areas of cellularity showing erythroid preponderence.	mcv-103,esr-50,vitamin B12-165,tsh-1.39,ana profile,anca & ana if -negative.	no follow up
bathirammal	I16040397	20	f	aplastic anemia	**bleeding per vagina,palpitation,fatigueability, bleeding gums,dyspnea+**	pallor+	2	3.7	7	normocytic normochromic,normocytic hypochromic to macrocytic normochromic - **anisopoikilocytosis+**	iron-32,tibc-312,ferritin-179	hypocellular bone marrow aspiration smears showing features of relative erythroid hyperplasia with haemophacytosis.	**hypocellular marrow** with consistent with aplastic anemia.	mcv-95,corrected reticulocyte count-1.68,vitamin b12-415,folate-5.11,idh-116,tsh-4.230,ft4-1.20,lft-normal,ana profile & ana if-negative.usg abdomen-mild hepatomegaly	1 month later hb-7.5,tc-7.6,plt-10
kaliammal	I17003600	63	f	Phemophagocytic lymphohistocytosis,acute infract in MCA territory	**fever,loss of appetite,loss of weight+**	pallor+,splenomegaly+	5.5	3.1	17	microcytic hypochromic anemia- **anisopoikilocytosis+**	iron-17,tibc-279,ferritin-631	imprint- cellular with mild preponderance of blast	**hypercellular marrow** with erythroid hyperplasia	mcv-65,esr-136,retic count-0.7,smear for mp-neg,ldh-505,uric acid-9.4,bilirubin[t]-0.7,[id]-0.3,[d]-0.4,protein[t]-6.1,alb-2.6,glo-3.5,urea-124,creatinine-2.64,tsh-0.42,protein electrophoresis-slight fall in albumin & slight rise in gamma globulins-usgg of inflammatory/infection.triglycerides-424,viral serology-neg,lepto,scrub & dengue-neg,ana profilr & ana if-negative.usg abdomen-splenomegaly+.mri brain-rt MCA territory infract.	refer to ipmer
hema	I17005886	35	f	dengue fever, sever iron deficiency anemia	**fever,headache,mylagia**	pallor+	6.3	2.5	90	not done	iron-13,tibc-418,ferritin-4	not done	not done	mcv-56,tsh-2.310,mcv-65.3,esr-21,dengue igM -postive,usg abdomen-normal.	no follow up
kalaiselvi	I17008174, I17007816	33	f	**hypersplenism**	**abdominal distension,loss of appetite**	pallor+,splenomegaly+	10	1.9	47	microcytic hypochromic anemia with leukopna & thrmbocytopenia-**anisopoikilocytosis +**	not done	corroborative with hypersplenism	**hypercellular bone marrow** with erythroid hyperplasia, there is no evidence of infiltrative or granulomas in the marrow studied.	mcv-83.4,esr-19,bilirubin[t]-0.6,[d]-0.3,[id]-0.3,sgpt-68,sgot-62,alp-226,protein[t]-5.5,alb-2.9,glo-2.6.spleen biopsy-benign vascular lesion s/o-diffusesinusoidal hemangiomatosis, liver biopsy-normal.usg abdomen-subtle coarse echotexture,dilated portal & spleenic vein,massive splenomegaly	10 days later hb-7.6,tc-7.1,plt-1231. 2 months later hb-9.2,tc-5.8,plt-488
arumugam	I17007272	69	m	megaloblastic anaemia- vitamin b12 & folate deficiency [mixed diet]	**easy fatigueability**	pallor+,icterus+	3.4	0.8	16	severe dimorphic anemia[microcytic hypochrmic to macrocytic normochromic] - **anisopoikilocytosis +,**elliptocytes+,schistocytes,tear drop cells,micro spherocyte,target cells,macroovalocyte,**polychromasia,gaint platelets.**	iron-188,tibc-200,ferritin-473	f/c/w megaloblastic anemia	**hypercellular marrow** with erythroid hyperplasia	mcv-97,rdw-39.7,mpv-8.0,esr-40,retic count-0.2,vitamin B12 -94,folate-1.56,idh-849,bilirubin[t]-1.7,[d]-0.6,[id]-1.1,protein[t]-5.6,alb-3.3,glo-2.3,usg abdomen-normal **(not done)**	no follow up
ramesh waran	I17008706	50	m	megaloblastic anaemia-vitamin B12 & folate deficiency [mixed diet]	**leg swelling,fatigueability**	pallor+,pedal edema+,hepatomegaly+,splenomegaly+	6.8	0.5	68	normocytic normochromic to macrocytic normochromic anaemia-**anisopoikilocytosis+,** macroovalocytes,tear drop cells ,**polychromasia**	iron-34,tibc-224,ferritin-1232	f/c/w -megaloblastic anemia	**hypercellular marrow** with erythroid hyperplasia	mcv-98.3,rdw-19.6,mpv-8.8,esr-64,vitamin b12-89,folate-0.96,bilirubin[t]-1.4,[d]-0.5,[id]-0.9,usg abdomen-hepatomegaly+,splenomegaly+ **[not done]**	no follow up
nathya	I17009192	25	f	megaloblastic anaemia-vitamin b12 & folate deficiency [mixed diet]	**fever,loose stools,fatigueability,**vomiting	pallor+,spleenomegaly+	4.1	3.5	37	macrocytic normochromic picture- **anisopoikilocytosis+, immature blast +,** hypersegmental neutrophils+,howell jolly bodies,basophilic stippling,microspherocytes,**polychromasia**,nucleated rbcs	not done	megaloblastic erythroid hyperplasia- megaloblastic anaemia	**hypercellular marrow** - megaloblastic erythroid hyperplasia	mcv-115,rdw-35.4,mpv-8.6,ldh-2830,reticulocyte count-5.4,tsh-4.630ft4-1.01,vitamin b12-<50,folate-0.76,usg abdomen-mild splenomegaly,duodenal biopsy-mild non specific duodenitis[grzade A reflux esophagitis, **normal**].	10 days later hb-10.6,tc-8.7,plt-403
arulalaan	I17009623	48	m	megaloblastic anaemia-vitamin b12 & folate deficiency + neuroendocrine neoplasm [veg]	**dyspnea,loose stools**	pallor+	4.6	2.9	45	macrocytic normochromic anaemia - **ansiopoikilocytosis,**hypersegmental neutrophils+,basophilic stippling,howell jolly bodies,elliptocytes,tear drop cells,schistocytes	iron-247,tibc-279,ferritin-451	erythroid hperplasia	**hypercellular marrow** - f/c/w megaloblastic anemia	mcv-124,rdw-17.1,mpv-9.7,esr-118,retic count-0.8,tsh-5.240,ft4-1.13,vitamin b12-69,folate-1.60,ldh-2267,usg abdomen-splenomegaly, duodenal biopsy - neuroendocrine neoplasm[scalloped duodenal folds,umbilicated lesion]	10 days later hb-8.2,tc-10,plt-164.2 months later hb-14.5,tc-13.5,plt-275

NAME	IP NO	AGE	SEX	DIAGNOSIS	SYMPTOMS	EXAMINATION	HB	WBC	PLT	PERIPHERAL SMEAR	ANAEMIA PROFILE	BA	BX	OTHER TEST	FOLLOW UP
musthafa	i17008568	57	m	? Aplastic anaemia	fatigueability,dyspnea,loss of appetite	pallor+	7.1	1.2	7	normocytic normochromic anaemia	not done	in adequate	hypoplastic marrow - ? Aplastic anemia	mcv-92,esr-129,urine benze zone proteins-neg,vitamin b12-556,folate-8.51,bilirubin [t]-1.4,[d]-0.8,[id]-0.6,proteins[t]-6.9,alb-3.1,glo-3.8,ldh-199,uric acid-3.0,tsh-0.705,viral serology-neg,ana profile-neg,ana if-neg,usg abdomen-fatty liver.	reffer to hematologist
padmavathi	i17009829	42	f	dimorphic anaemia-severe iron deficiency anaemia & vitamin b12 deficiency	fatigueability,palpitation,facial puffiness,pedal edema,dyspnea.	pallor+,pedal edema+	3.5	2.2	95	microcytic hypochromic anaemia- anisopoikilocytosis+, normal	iron-8,ferritin-2,tibc-493	erythroid hyperplasia ,megaloblastosis, and gaint myeloid precursors.scattered megakaryocytes.	hypercellular marrow - erythroid & megakaryocytes hyperplasia	mcv-62,rdw-22.2,mpv-8.6,esr-66,sob-neg,vitamin b12-138,folate-8.22,duodenal biopsy-normal[lax lower esophageal sphincter,,normal],usg abdomen-mild spleenomegaly	2 months later rpt hb-7.9,tc-3.5,plt126
parvathi	i17010456	40	f	megaloblastic anaemia-vitamin b12 deficiency, atropic gastritis [vegetarian]	fatigueability,dyspnea, palpitation	pallor+,jcterus+,pedal edema	3.8	3.9	22	macrocytic anaemia with thrmbocytopenia- anisopoikilocytosis +, hypersegmented neutrophils+, occasional immature wbc+,polychromasia	iron-31,tibc-365,ferritin-1018	f/s/o-megaloblastic anaemia	hypercellular marrow - megaloblastic erythroid hyperplasia & megakaryocytic hyperplasia consistent with the peripheral anaemia	mcv-101,rdw-26.4,mpv-8.7,esr-120,vitamin b12 -<50,folate>20,bilirubin[t]-2.1,[d]-1.4,[id]-0.7,sgpt-39,sgot-162,alp-126,tsh-1.370,ft4-1.13,idh-7433, d dimer-5.6,ana profile- neg,rf-neg,ana if-postive [fine cytoplasmic speckles jo 1 patern,nuclear pattern+],anti leptospira -neg,usg abdomen - hepatomegaly,spleenomegaly+, duodeneal biopsy-foveolar metaplasia[atropic gastritis,scalloping duodenal folds].	10 days later hb-7.1,tc-5.6,plt-230
ramayee	i17007743	57	f	hypersplenism,non cirrhotic portal fibrosis,portal hypertension,oesophageal varices	bleeding gums,epistaxis, fatigueability	pallor+,hepatosplenomegaly	4.4	2.7	98	microcytic hypochromic anaemia with eosinophilia -anisopoikilocytosis +	not done	not done	hypercellular marrow - with erythroid hyperplasia and megaloblastic changes	mcv-83,esr-45,bilirubin[t]-0.4,[id]-0.1,[d]-0.3,liver biopsy- liver biopsy-f/c/w-non cirrhotic portal hypertension	
vasanth	i17009680	39	m	iron deficiency anaemia, dengue fever	fever,headache,tiredness,cough with expectoration	pallor+,hepatomegaly+	4.7	2.7	60	microcytic hypochromic anaemia - anisopoikilocytosis+	iron-12,tibc-414,ferritin-10	f/c/w-iron deficiency anaemia. There is marked megakaryocyte hyperplasia corresponding to peripheral thrmbocytoenia	normocellular marrow - in sufficient	mcv-58,esr-36,retic count-0.7,vitamin b12-427,folate-5.88,tsh-0.43,hiv,hbsag,hcv were negative,dengue ns 1 ag-postive,ana prfile-neg, usg abdomen-prominent hepatic veis & ivc,mild splenomegaly	10 days later rpt hb-9.1,tc-5.2,plt-410
ammasai	i17011294	85	m	megaloblastic anaemia- folate deficiency [veg]	dyspnea,slurring of speech,fatigueability	normal	4.7	3.9	43	macrocytic normochromic anaemia - anisopoikilocytosis+,hypersemental neutrophils+,lymphocytosis+,carbot ring,basophilic stippling,elliptocyte,tear drop cells,macroovalocyte,nucleated rbc,gaint platelets	iron-178,tibc-259,ferritin-277	f/c/w-megaloblastic anaemia with ineffective haematopoiesis	hypercellular marrow with erythroid hyperplasia	mcv-91,rdw-19.0,mpv-10.1,retic count-1.5,esr-95,vitamin b12->2000,folate-<0.600,,idh-2018,,bilirubin[t]-2.9,[d]-0.5,[id]-2.4,tsh-1.46,haptoglobin-15.5,dengu serology-neg,scrub - neg,hiv- neghbsag-neg,hcv-neg,usg abdomen-mild splenomegaly, [not done]	15 days later rpt hb-12.1,tc-5.7,plt-189
gayathri	i17012639	25	f	dengue fever,non cirrhotic portal fibrosis,hypersplenism	fever,vomiting,mylagia,headache	pallor+	9.7	0.7	33	hypochromic anaemal - anisopoikilocytosis+	not done	not done	hypercellular marrow - with micronormoblastic erythroid hyperplasia	mcv-75,esr-43,dengue igm-postive	1 month later rpt hb-11.1,tc-3.9,plt-47
muthuvelappan	i17013571	65	m	megaloblastic anaemia- folate deficiency [mixed diet]	paraesthesia of b/l foot,loss apoetite,fatiueabiltv	pallor+	3.8	3.4	88	pancytopenia with macrocytosis of rbc - anisopoikilocytosis,activated lymphocytes+,ovalocytes,tear drop cells,schistocytes,saint platelets	not done	diluted	hypercellula marrow - erythroid hyperplasia	mcv-112,rdw-17.6,mpv-8.3,idh-3827,esr-115,corrected retic count-0.3,usg abdomen-cholelithiasis,minimal rt pleural effusion,vitamin b12->2000,folate-4.18,ldh-3827,ugi scopy-bile reflux gastritis,mild scalloped duodenal folds,duodenal biopsy-trpical spure[scalloped duodenal folds],mri brain-multiple areas of periventricular white matter hyper intensities predominently in the peri callosal reaion & subcortical white matter in LT parietal lbe	
pavithra	i17010398	18	f	dengue hemorrhagic fever,viral infection induced hemophagocytic lympho histiocytosis [secondary HLH syndrome],coexisting cmv & ebv infection.	fever,vomiting, mylagia	pallor+	8.7	1.8	60	microcytic hypochromic anaemia - anisopoikilocytosis+, activated lymphocytes+	iron-26,tibc-327,ferritin->2000	erythroid hyperplasia & haemohagocytosis	normocellular marrow - erythroid hyperplasia	mcv-56,esr-8,corrected retic count-4.02,bilirubin[t]-1.9,[d]-1.5,[id]-0.4,sgpt-460,sgot-1055,alp-269,protein[t]-4.5,alb-2.4,glo-2.1,ldh-3517,triglyceride-966,tsh-4.580,ft4-1.38,haptoglobin-46.4,dengue igm postive,viral serology - negative,liver profile igG-negative,ana profile-neg,ana if- dense fine speckles,cmv igm - postive, ebv igg postive,usg abdomen-altered echotexture of liver,mild ascities,b/l mild pleural effussion.	8 days later rpt hb-10.2,tc-8.9,plt-186.2 months later -rpt hb-11.7,tc-5.8,plt-298.rpt sgpt-46,sgot-35,triglyceride-125,ferritin-361
radhakrishnan	i17016170	56	m	myelodysplastic syndrome	blisters over extrimities,fever,cough with expectoraton	pallor+,pedal edema,blisters+	8	3.9	20	f/o-intracascular haemolysis - predominantly microcytic hypochromic picture,hypersegmental neutrophils+,immature wbc+,anisopoikilocytosis+	not done	f/s/o-megaloblastosis & dyspoiesis	hypercellular marrow - possibility of myelodysplastic syndrome[RAEB-refractory anaemia with excess blast]	mcv-73,esr-25,corrected rectic count-0.5,urine test postive for haemoglobinuria/myoglobinuria,HAMSA TEST -NEGATIVE, SUCROSE LYSIS TEST -negative,ldh-466,uric acid-2.9,c3-56,c4-12,haptoglobin-138,ferritin-1152,cryoglobulin-1.4,tvitamin b12->2000,folate-14.99,viral serology-neg,ana profile -neg,ana if-neg,anca-neg.usg abdomen-moderate ascites,b/l small pleural effusion.direct coombs test-wealky postive,flow cytometry for CD55 & CD 59 was negative.skin biopsy-leukocytoclastic vasculitis.	
palanisamy	i17016803	69	m	lymphoma - non hodgkins lymphoma	loss of appetite,fever	pallor+,hepatomegaly,splenomegaly	7.7	1.5	81	pacytopenia with activated lymphocytes+ - normocytic normochromic to macrocytic normochromic	iron-19,tibc-178,ferritin-670	f/s/o-lymphoplasmacytic infiltrate in the marrow suggest the following possibilities - lymphoplasmacytic lymphoma & small b cell lymphoma with plasmacytic differentiation	hypocellular marrow - lymphoplasmacytic infiltrate in the bone marrow - lymphoplasmacytic lymphoma & small b cell lymphoma with plasmacytic differentiation	mcv-97,esr-96,ldh-209,viral serology-neg,usg abdomen-hepatosplenomegaly,dilated portal vein,gall bladder sludge,prostatomegaly. Creat-1.21,bilirubin [t]-0.7,[d]-0.4,[id]-0.3,protein [t]-7.1,alb-2.8,glo-4.3.	reffer to higher centre
sadhasivam	i17017488	43	m	megaloblastic anaemia-vitamin b12 deficiency [veg]	fever,loose stools, vomiting, fatiueability,breathine difficulty	pallor+,jcterus+	4	2	33	microcytic hypochromic to macrocytic normochromic - anisopoikilocytosis +, hypersegmental neutrophils+ & lymphocytosis +,elliptocytes,tear drop cells,macroovalocytes,spherocytes,basophillic stippling,nucleated rbc	not done	hypercellular marrow & shows megaloblast in plenty - megaloblastic anaemia with ineffective haemotopoiesis	hypercellular marrow with meaoloblastic maturation	mcv-119,rdw-42.0,mpv-9.2,esr-2,corrected retic count-0.5,bilirubin [t]-3.6,[d]-0.4,[id]-3.2,protein[t]-7.0,alb-3.9,glo-3.1,haptoglobin-<10,idh-4689,tsh-2.170,creat-1.38,uric acid-9.8,vitamin b12 - 80,folate-6.63, ana profile-neg,ana I - nee. viral serology,usg abdomen-cholelithiasis [not done]	2 months later-hb-11.8,tc-5.4,plt-224
balamani	i17020269	61	f	megaloblastic anaemia-vitamin b12 deficiency [veg]	fatigueability+,loss of appetite,weight loss+	pallor+	4.5	2.1	98	macrocytic normochromic & microcytic hypochromic anaemia - anisopoikilocytosis+,elliptocyte,schistocyte,tear drop cells,gaint platelet.	iron-101,tibc-222,ferritin-112	hypercellular with erythroid hyperplasia - megaloblastic anaemia with ineffective haematopoiesis	f/s/w-megaloblastic anaemia - hypercellular marrow	mcv-92,rdw-36.3,mpv-8.3,esr-80,retic count-0.8,bilirubin [t]-1.3,[d]-0.4,[id]-0.9,protein[t]-6.7,alb-4.0,glo-2.7,,idh-5126,tsh-4.80,usg abdomen- normal [not done]	no follow up
rukumani	i17023135	65	f	aplastic anaemia	headache,fever,vomiting	pallor+,b/l lower limb petechiael spots+	4.7	2.2	3	pancytopenia- anisopoikilocytosis+, activaed lymphocytes+	iron-249,tibc-271,ferritin-463	haemodiluted- few atypical cells +	hypoplastic bone marrow with patchy erythroid & lymphoid siland.	mcv-109,esr-100,vitamin b12-200,folate-12.85,ldh-166,bilirubin [t]-0.7,[d]-0.3,[id]-0.4,protein [t]-6.9,alb-3.9,glo-3.0,haptoglobin-107,uric acid-5.4,cea-1.3,ca-125-10.63,ca 19-9-11.9,afp-2.0,ana profile-neg,ebv igG-postive,cmv-neg,ana if - neg,dengue ns1 -neg,usg abdomen-normal,parvo virus b19-neg.	7 days later hb-7.7,tc-6.5,plt-3
kalliappan	i17027238	87	m	megaloblastic anaemia-vitamin b12 [mixed diet]	fever,mylagia,loose stools,abdominal pain,altered sensorium	disoriented	9.1	0.9	54	macrocytic normochromic anaemia - anisopoikilocytosis+, activated lymphocytes+,elliptocyte,target cells,	not done	megaloblastic anaemia bone marrow aspirate	normocellular marrow - trilineage haematopoiesis with megaloblastic erythropoiesis	mcv-107,rdw-18.6,mpv-8.7,esr-55,smear for mp-neg,bilirubin [t]-0.5,[d]-0.2,[id]-0.3,protein [t]-5.5,alb-3.2,glo-2.3,uric acid-2.5,vitamin b 12-<50,folate-7.62,tsh-0.635,protein electrophoreisis-normal pattern,hiv-neg,ana if- neg,dengue ns1 - neg,usg abdomen-normal study [not done]	???????????
annakodi	i17027161	35	f	megaloblastic anaemia-vitamin b 12 & folate deficiency [mixed diet]	fatigueability,loss of appetite,loss of weight	pallor+	4.8	3.7	55	pancytopenia with macrocytes of rbc - anisopoikilocytosis+, tear drop cells,ovalocytes	iron-62,tibc-219,ferritin-67	megaloblastic anaemia with ineffective haematopoiesis	hypercellular marrow - with predominant megaloblastic erythroid hyperplasia	mcv-110,rdw-30.0,mpv-9.1,esr-1,corrected retic count -0.2,vitamin b12 -<50,folate-1.43,tsh-1.94,idh-4631,,bilirubin [t]-1.0,[d]-0.2,[id]-0.8,protein [t]-6.6,alb-3.6,glo-3.0,viral serology-neg,dengue ns1-neg,ana profile-neg,usg abdomen-normal, [not done]	???????
jayasudha	i17027129	31		systemic lupus erythematosus with lupus nephritis	facial puffiness & leg swelling	pallor+,pedal edema+,periorbital edema	3.4	2.9	64	normocytic normochromic to microcytic hypochromic anaemia - anisopoikilocytosis+	iron-30,tibc-110,ferritn-1702	haemodiluted	hypercellular marrow space, there is erythroid hyperplasia - trilineage hematopoiesis	mcv-79,ana profile- sm postive,nucleosomes posive, histones postive, ana if postive- nucleus fine speckled+++,dense fine speckled cytoplasm+++. Renal bioby-lupus nephritis class iv [a]-isn/rps classification 2004,c3-<30,c4-<4, vitamin b12->2000,folate-3.75	
palanimmal	i17030045	62	f	non hodgkin lymphoma - follicular lymphoma	fever,leg swelling,loss of appetite,dyspnea	pallor,pedal edema+,oral thrush+	5.7	3.7	99	normocytic normochromic anaemia - anisopoikilocytosis+	iron-30,tibc-139,ferritin-660	trilineage hematopoiesis with erythroid preponderance showing micronormoblast [?iron deficiency]	hypercellular marrow space - erythroid hyperplasia	mcv-77,esr-88,uric acid-17.3,ldh-631,vitamin b12->2000,folate-24.9,tsh-0.647,cervical lymph node biopsy-atypical lymphoid cells strongly express CD20 [b cell marker] & bcl imunostain, the surrounding reactive lymphocytes shows CD3 postivity[t cell marker], ki67 [proliferative marker] is high >60%	
tharrun kumar	i17029284	19	m	systemic lupus erythematosus	fever+,sore throat+,loss of weight, loss of appetite	oral ulcers+,b/l cervical lymph node+	9.9	3.3	45	mild normocytic normochromic anaemia - lymphocytosis+, activated lymphocves+	not done	normal erythroid & myeloid precursors cells.scattered macrophages with haemophagocytosis are observed	normocellular marrow - megakaryocyte hyperplasia,there are no abnormal cells or eranulomas in the sections studied	mcv-78,esr-90,ana profile-sm ++,nucleosome ++,histones++.	
nagarathinam	i16022322	65	f	ulasma cell dvscrasias - meus	fever+,dvsonea.fatiueabiltv	pallor+	3.9	2.9	6	anisopoikilocytosis+, lymphocytosis+	iron-122,ferritin-319,tibc-221	erythroid hyperplasia & plasmacytosis - plasma cell dyscrasia	inadequate - mild plasmacytosis	mcv-96,esr-140,urine for bence jones proteins -neg,tsh-6.63,vitamin b12-568,folate->20,protein electrophoresis - mild elevation in gamma globulin-no abnormal band is seen.ana if-negativee,usg abdomen-fatty liver,beta 2 microglobin-2740[high],immunoglobulin total igg-16.90,serum light chain - kappa 59.20[hieh]. lambda-39.60 [hieh]	
najmudeen	i17027965	45	m	megaloblastic anemia - vitamin b12,folate deficiency [mixed diet]	fever,loose stools	pallor+	5.8	2.4	90	macrocytic normochromic anemia - lymphocytosis +, hypersegmental neutrophils+,basophillic stippling,howell jolly bodies,nucleated rbc,	iron-142,tibc-193,ferritin-506	f/c/w -megaloblastic anemia	hypercellular marrow space- f/c/w- megaloblastic anemia	mcv-128,rdw-21.0,mpv-9.4,vitamin b12-<50,folate-1.25,deep duodenal biopsy-c/w tropical spure[duodenal villous atrophy]	
baskar	i17033639	48	m	megaloblastic anemia - vitamin b12 & folate deficiency[mixed diet]	fatigueability	pallor+,hyperpigmentation + over palm, splenomegaly+	4.4	2.3	64	pancytopenia with macrocytosis - anisopoikilocytosis+,macroovalocytes,tear drop cells,schistocyte,	iron-263,tibc-272,ferritin-1808	f/c/w-megaloblastic anemia	hypercellular marrow space- megaloblastic erythroid hyperplasia	mcv-133,rdw-19.1,mpv-10.8,idh-1034,vitamin b12-162,folate-<0.600, usg abdomen - mild splenomegaly, duodenal biopsy - tropical sprue[normal mucoasal study]	
subramani	i17032954	47	m	chronic liverdisease with portal hypertension, megaloblastic anemia - vitamin b12 deficiency[mixed diet]	fatigueability,dyspnea,weight loss+	pallor+,splenomegaly+	4.8	1.6	25	pancytopenia with macrocytosis and atypical cells 3% - anisopoikilocytosis+,hypersegmental neutrophils+, immature wbc+	iron-63,tibc-329,ferritin-496	megaloblastic erythropoiesis	hypercellular marrow	mcv-101,rdw-16.2,mpv-9.3,vitamin b12-<50,folate-1.4,bilirubin [t]-1.8,d-0.6,id-1.2,usg abdomen-liver parenchymal disease with portal hypertension,moderate splenomegaly.deep duodenal biopsy -tropical spure[pedunculated polyp stomach]	